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PAVLOVIAN CONFERENCE ON HIGHER NERVOUS ACTIVITY

Conference Editor
NATHAN S. KLINE

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CONTENTS

* This series of papers is the result of the *Pavlovian Conference on Higher Nervous Activity* held and sponsored conjointly by The New York Academy of Sciences of the United States of America and The Academy of Medical Sciences of the Union of Soviet Socialist Republics on October 13, 14, and 15, 1960, in New York, N. Y. The conference and the publication of these papers were supported in part by Grant MY-4417 from the Psychopharmacology Service Center of the National Institute of Mental Health, Public Health Service, Bethesda, Md. The monograph will be published in Russian by The Academy of Medical Sciences of the Union of Soviet Socialist Republics.

Part II. Cortico-Subcortical Interaction

Part III. Deviance and Drugs

Part IV. Irradiation and Generalization

Part V. Psychopharmacology

Part VI. Inhibition

FOREWORD

Nathan S. Kline
Rockland State Hospital, Orangeburg, N. Y.

This publication comprises the proceedings of the first joint meeting of a Soviet scientific academy and an American one. In the face of ambivalent and unpredictable relationships existing between the representatives of the two countries at the United Nations, a few blocks away from Town Hall, where the conference on which this monograph is based took place, the activities throughout the symposium were cordial, open, and informative.

Tremendous gratitude is due to numerous individuals, including especially V. V. Zhdanov, Learned Secretary of the Academy of Medical Sciences of the Union of Soviet Socialist Republics in Moscow and D. John Heyman, Project Coordinator at the Rockland State Hospital Research Facility, Orangeburg, N. Y.

Hopefully this is only the first of a series of Pavlovian conferences and possibly only the first of joint conferences on other pertinent scientific subjects. In a world that is seeking to understand and orient itself, knowledge of each other's frame of reference is crucial. Knowledge does not require acquiescence but is at least a first step toward agreement. May the promise reach fulfillment.

INTRODUCTORY REMARKS

Gregory Razran
Queens College, Flushing, N. Y.

The very name Pavlovian strikes a chord of many overtones, rings be varied in timbre—and signalization. Ivan Petrovich Pavlov was surely one history's greatest thinkers and researchers in one of man's most unsolved—y most needed to be solved—problems: the integration and interrelation of brai behavior, and mind. Pavlov was a great innovator, a pathfinder for ne truths, new methods, new concepts, and new philosophies; he was a radic transformer of our basic thoughts on the role of man in nature and the role mind in man, on ways of controlling man and mind, and on ways of unde standing man and mind.

Pavlov himself modestly paid generous tribute of precedence to Jacqu Loeb, Herbert Jennings, and Edward Thorndike, but I feel that I am not di respectful to the memory of these distinguished United States scientists if accord to Pavlov the status of the chief architect of the entire idea syster Modern scientific American behavioral psychology and behavioral sciences general simply could not operate their research and thoughts without such co cepts as Pavlov's conditioning, extinction, generalization, differentiation, i hibition, disinhibition, higher order conditioning, compound conditionin orienting and vigilant reactions, experimental neurosis, and second-sign systems.

Almost our entire methodological armamentarium and most of our codes explanatory principles are deeply set in what Pavlov did and said. Frequent research colleagues, discussing some new finding in the kaleidoscope of th dynamics of behavior, have said or written to me: "You know, if you read car fully Pavlov's two books, you will find somewhere some indication or som explanation of what I found." American behavioral scientists have sure added wings to the house that Pavlov built, but really only wings; the ma house continues to overtower and to stand firm, little worn by wind ar weather.

The two Pavlov books that American scientists discuss or quote—or crit cize—were translated into English in the 1920s: one in 1927 by G. V. Anre of Oxford University, Oxford, England and one in 1928 by W. Horsley Gant who contributes to this monograph. The books' translations and Pavlov death in 1936 were followed by the brilliant researches of Ivan Solomonovic Beritashvili, Leon Abgarovich Orbeli, Konstantin Mikhailovich Byko Vladimir Nikolayevich Chernigovsky and, among the distinguished contribu tors to these pages, Pyotr Kuz'mich Anokhin, Ezras Asratovich Asratya Pyotr Stepanovich Kupalov, Oleg Vasilevich Kerbikov, Andrey Vladimirovic Snezhnevsky, Vasily Vasilevich Zakusov, and many others whose work is st largely terra incognita in the United States.

The war and the special postwar developments have converted a langua barrier into a thought barrier in an area in which no barriers should or cou

exist. It is thus the purpose of this monograph to attempt to lift the barriers, to open the dam, so to speak, and let knowledge flow freely from one country to the other. Let knowledge cover the earth as water fills the sea, to paraphrase a not wholly unfamiliar quotation, I hope, from *Isaiah* on wisdom, peace, and friendship.

In planning the conference on which this monograph is based The New York Academy of Sciences, in a sense, proposed, and the Academy of Medical Sciences of the Union of Soviet Socialist Republics disposed. What I mean is that originally we suggested a conference that would embrace all phases of Pavlov's system, including visceral action, verbal behavior, child behavior, perception, psychotherapy, and social and philosophical implications. The Soviet Academy thought, however, that the conference should be the first of a series, and that wê should thus begin with the beginning, confine ourselves to the area in which brain and behavior are most intimately related—neural aspects—and leave the more complex aspects of brain and mind to future occasions. I believe that this disposition of our program is a correct one, not only because of the basic nature of the neural aspects but also because of the common fallacy that Pavlovian physiologists deal only with a conceptual-hypothetical nervous system and not with one that is directly observable and experimentable. The contributions to this publication of so many distinguished American scientists whose signal research and outstanding contributions to the field are based on direct neural observations refute, of course, this fallacy, and the papers of the Soviet contributors will, I am sure, dispel it completely.

And now let me say a few words to our Soviet colleagues in their own language: Добро пожаловать, многоуважаемые коллеги! Надеемся что наша совместная конференция послужит начальным звеном в цепи продуктивных контактов и взаимодействий в общей нам науке. Наука не знает географических границ и не терпкт, не легко терпит, ограниченийч еловеческого ума в поисках истины и знаний.*

* Welcome, esteemed colleagues: let us hope that this joint conference will become the first link in a chain of future fruitful contacts and interactions in our common science. Science knows no geographical boundaries and knows no bounds for man's mind in search for truth and knowledge.

Part I. Structure and Function

RECENT CONTRIBUTIONS TO THE ELECTRO-PHYSIOLOGY OF LEARNING

H. W. Magoun
Department of Anatomy, School of Medicine, University of California, Los Angeles, and Veterans Administration Hospital, Long Beach, Calif.

It is a great pleasure to be able to participate in this international discussi sponsored jointly by The New York Academy of Sciences and The Academ of Medical Sciences of the Union of Soviet Socialist Republics. In so doin I propose first to survey some of the recent Western advances in this field ar then consider important current Soviet contributions to knowledge of th Pavlovian orienting reflex, which might not otherwise be represented in the pages.

The most striking recent progress in the biology of higher neural activity ha unquestionably come from electrophysiological analysis of the mechanism learned behavior. Knowledge has been advanced especially by a marria between the electrical recording techniques of Western neurophysiology ar the classic Pavlovian approaches to the study of conditional reflexes cultivate so extensively in the Soviet Union. Such developments have formed the sub ject of a number of recent international meetings, among which have been th Moscow Colloquium on Electroencephalography and Higher Nervous Acti ity,[12] the Montevideo Symposium on Brain Mechanisms and Learning,[25] ar the Macy Conferences on the Central Nervous System and Behavior.[2]

Electrocortical Conditioning

While pioneering studies of the electrical activity of the brain during lear ing were undertaken in the Union of Soviet Socialist Republics by M. I Livanov and A. B. Kogan beginning in the 1930s, and more recently have bee extended by a considerable number of Soviet investigators, as reviewed b Rusinov and Rabinovich,[24] these findings are just now becoming available English translation, and Western knowledge of them is still regrettably limite

Western studies in this field similarly began in the 1930s when Durup ar Fessard,[5] during study of the alpha-blocking response to visual stimulatio noted that an associated click of their camera soon itself elicited blocking eve when the visual stimulus was not presented. Their adventitious finding w confirmed and extended by Jasper and Shagass[11] and by other investigator More recently the method has been employed, particularly by Morrell and h associates,[17-21] as a means of studying the formation of temporary connectio in the brain during simulated conditioning procedures.

Such "learned" blocking of the alpha rhythm is illustrated in FIGURE from Morrell and Ross.[17] An initial lack of cortical response to a tone (th signal line, in A) can be contrasted with the unconditional blocking of t occipital alpha rhythm induced by a bright light stimulus (thick signal lir in B). In the first paired trial (C), the lack of response to the tone again co

trasts with the alpha blocking when the light appears. By the ninth trial (D), however, alpha blocking occurs in response to the tone before the light stimulus is presented. At this initial stage, conditional alpha blocking is displayed widely over the cortex; subsequently, it becomes confined to the occipital region, that is, to the projection area of the unconditional signal.

These observations of electrocortical conditioning confirm the conclusion of Pavlov that, by study of what he called "higher nervous activity," it is possible not simply to understand the performance of the brain but to change it: a contribution with the potentiality of becoming the most powerful ever made by science. By appropriate association and repetition of two signals, a previously indifferent, conditional stimulus can ultimately evoke the response initially induced only by unconditioned stimulation.

As Pavlov proposed, novel functional connections must be established to subserve this "learned" behavior. Appropriately, these records of conditioned

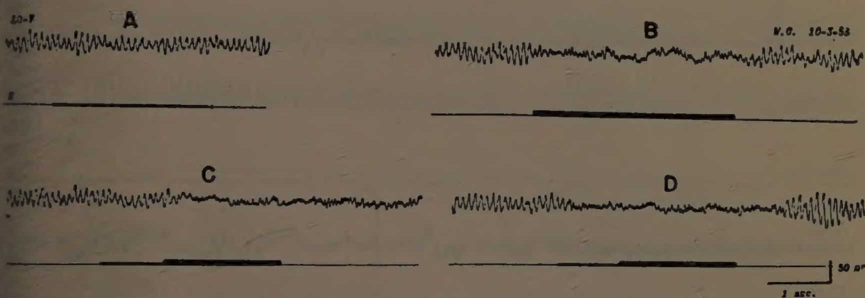

FIGURE 1. Records of electrical activity from the brain of a normal human subject, illustrating the establishment of a conditional blocking of occipital alpha rhythm. The initial lack of response to a tone stimulus (thin black signal) is seen in A. The unconditioned alpha blockade to bright light stimulation (thick black signal) is seen in B. When the signals are first paired (C), the tone stimulus preceding the light is ineffective. By the ninth trial, in D, however, the tone stimulus evokes a conditional alpha-blocking response before the light appears. From Morrell and Ross;[17] reproduced by permission from the *A. M. A. Archives of Neurology and Psychiatry.*

electrical activity were obtained from the cortex of the cerebral hemispheres which, according to Pavlov, was the pre-eminent site of formation of such novel, adaptive, temporary, conditional neural links. Furthermore, the consecutive alterations of electrocortical events, at first widespread and subsequently focal, appear to parallel the succession of initial generalization and later differentiation that was identified by Pavlov in the establishment of a conditional reflex. Additionally, the observation that recordable alterations are most conspicuous in the cortical analyzer, or receiving area, for the unconditioned signal suggests the possibility that it may be the dominant focus of the change.

In general, then, these electrophysiological studies seem significant in confirming, inside the brain, some major features of Pavlov's concepts of conditional reflex activity, drawn chiefly, and of necessity because of the state of technical development at his time, from observations of peripheral behavior. This present ability to investigate the learning process directly, by recording the activity of central neural aggregates in which it is taking place, holds the promise of providing real insight into its mechanism.

Further efforts in this direction have stemmed from a later variation of electrocortical conditioning, in which Morrell and Jasper[18] employed intermittent rather than steady photic stimulation as the unconditional stimulus; at the stage between the initial general and the final focal desynchronization of the EEG they observed in the visual cortex, and again in the focus of the unconditioned analyzer, a tone-induced repetitive response the frequency of which was

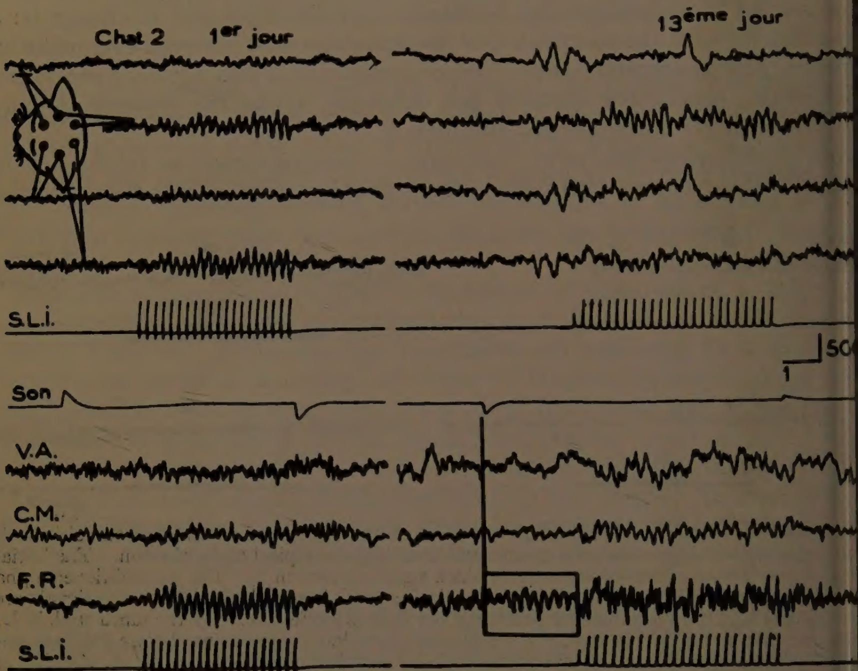

FIGURE 2. Records of electrical activity in cortical and subcortical regions of the cat brain, showing responses to tone (SON) and intermittent photic (SLI) stimulation. On the first day (*left*), the sound is without effect, and one observes only the unconditioned driving of the occipital and reticular activity at the frequency of the light flashes. On the 13th day, however, the sound evoked a conditional response at the same frequency as the rhythmic light flashes, recorded only from the reticular formation. The first four channels record activity from frontotemporal and temporo-occipital regions, and the lower three from the thalamic nucleus ventralis anterior (VA), the centre median (CM), and the mesencephalic reticular formation (FR). From Yoshii, Pruvot, and Gastaut;[31] reproduced by permission from *Electroencephalography and Clinical Neurophysiology*.

that of the photic stimulus (FIGURES 2, 3). These experiments with intermittent photic stimulation were extended by Yoshii and his co-workers,[29-32] who found that the conditioned repetitive discharges were earlier in onset, higher in amplitude, and more constant in subcortical structures, especially in the mesencephalic reticular formation. In a subsequent study, Yoshii and Hockaday found that this conditional, frequency-specific response was prevented by bilateral lesions in nonspecific thalamic nuclei; interference with conditioning following lesions of the diencephalon and midbrain similarly has been reported by Doty.[4] Morrell[20,21] likewise has supported the involvement of nonspecific

mechanisms of the brain stem in electrocortical conditioning. It is his view that the initially generalized pattern of activation is mediated by the mesencephalic reticular system, while subsequent focal EEG activation, limited to the receiving area for the unconditional stimulus, is subserved by intralaminar and midline thalamic nuclei.

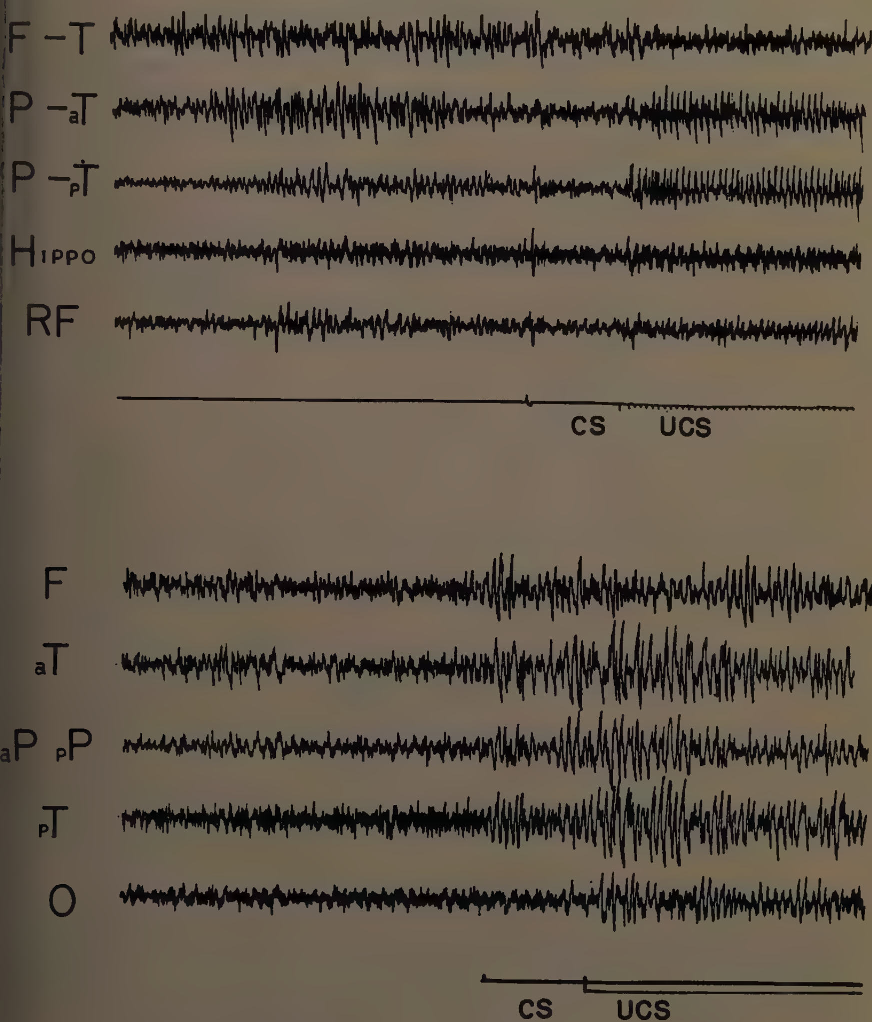

Figure 3. Records of electrical activity in cortical and subcortical regions of the cat's rain show (*above*) an initial absence of response to a tone stimulus (cs) and a frequency-specific ischarge to an unconditioned seven-per-second photic stimulus (ucs). On the next day (*below*) the conditional tone stimulus evokes widespread frequency-specific responses in the cortex. he channels record from frontal (F), parietal (P), temporal (T), and occipital (O) cortical gions, and from the hippocampus (Hipp) and midbrain reticular formation (RF). From oshii and Hockaday;[32] reproduced by permission from *Electroencephalography and Clinical europhysiology.*

In similar fashion it has been proposed by Gastaut[7,8] that closure in cond tional learning is not completed within the cortex, for sectioning between th cortical analyzers or removal of one of them does not prevent closure. A ternatively, Gastaut proposes that closure is established at the sites of conve

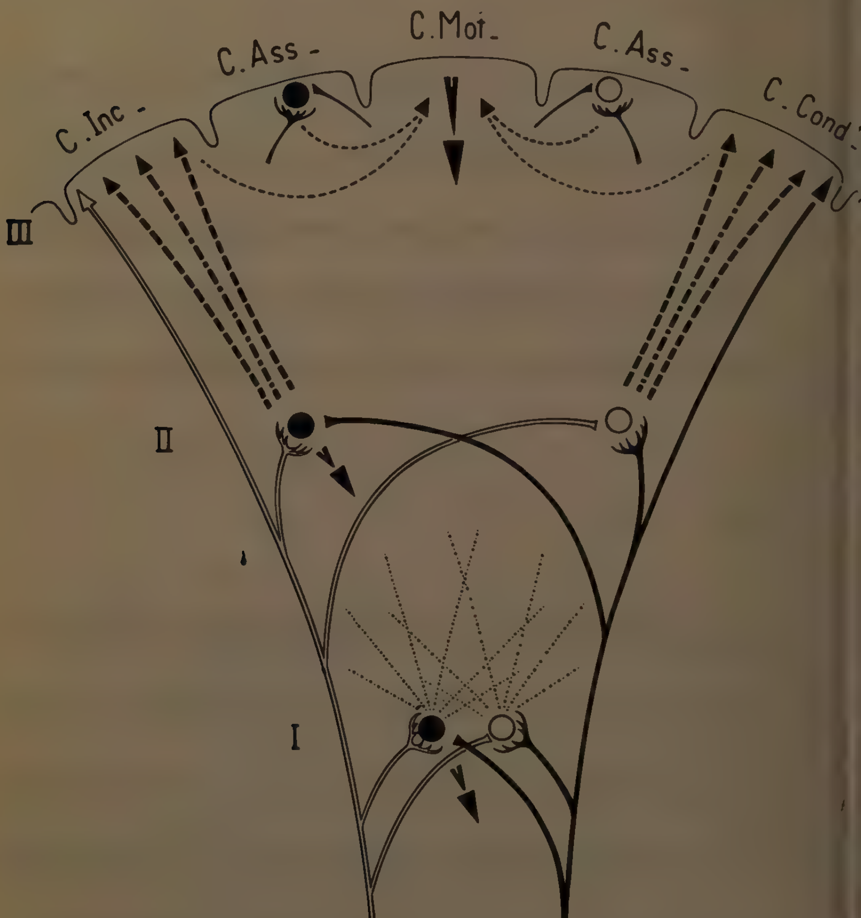

FIGURE 4. Diagram of the proposed subcortical and cortical levels of the brain involve in the formation of a conditional reflex. Key: I, the midbrain reticular formation; II, thal mus; III, cortex. The white pathway (*left*) is that of the unconditioned stimulus (S); th black path (*right*), that of the conditional stimulus (s). The circles represent reticular neuro on which the heterogeneous stimuli converge. The unconditioned (C-Inc), the condition (C-Cond), associational (C-Ass), and motor (C-Mot) cortical areas are shown. From Ga taut;[8] reproduced by permission from *The Neurological Basis of Behavior*.

gence of signals within the reticular formation or the nonspecifically projectin thalamic nuclei of the brain stem. As seen in FIGURE 4, he conceives of th setting up of a focus of excitation in the reticular formation by way of colla erals from the afferent paths for the unconditional stimulus, with the establish ment of connections between it and the cortex, and with the subsequen

domination of localized thalamocortical projections over more diffuse ones from lower levels as the ultimate changes become focal rather than generalized.

Paradoxically, these developments of Western neurophysiology, concerned initially with study of the electrical activity of the cerebral cortex, have thus served to emphasize the importance of convergence of signals in the central brain stem, in proposing a subcortical rather than a cortical genesis of the learning process.

Reinforcement

Additional Western emphasis upon the importance of subcortical mechanisms has come from study of the role of reinforcement in learning, but in quite a different sense. Valuable progress has been made by monitoring tracer responses evoked in central neural stations by afferent stimulation, before and during reinforcement procedures. In the experiments of John and Killam,[14] novel photic stimuli, which initially evoked widespread high-amplitude central activity, were repeatedly presented, unpaired with any consequence, until the amplitude of evoked potentials became reduced and their distribution confined to the visual pathway, a stage described as habituation (FIGURE 5*a*). Immediately thereafter, when negative reinforcement was introduced by pairing shocks to the feet with the tracer stimuli, central responses again became widely generalized and displayed a marked increase in amplitude (FIGURE 5*b*). In similar experiments of Galambos[6] and of Hearst *et al.*,[9] tone-evoked responses in the hippocampus were conspicuously augmented when positive reinforcement was introduced (FIGURE 6).

These recent findings, along with those of Jouvet and Hernández-Peón,[15] of Hernández-Peón *et al.*,[10] and of Worden[28] demonstrate the important role of reinforcement in increasing the amplitude and generalizing the distribution of afferent signals in the reticular and limbic mechanisms of the brain. It is possible, however, that these events may be related to the orienting reflex or the reinforcing process and contribute importantly to the genesis of learning, disappearing once it has become established, without themselves representing specific features of the formation of temporary connections in deep-lying regions. Moreover, the average-response analysis of Brazier[3] has shown that, even without reinforcement, afferent potentials evoked in unanesthetized animals are much more widely distributed in the brain than previous concepts of modality segregation allowed. From these studies, it would no longer seem necessary, in accounting for the establishment of temporary connections, to search for limited sites of convergence between otherwise isolated signals. During reinforcement, in particular, the problem would seem rather to lie in determining in which of many possible regions new functional relationships may become established. It has even been proposed that central reinforcement systems be given a significance equivalent to that of the analyzers in conditional reflex theory.[16]

Orienting Reflex

In contrast to those in the West, recent developments in the Soviet Union have been based upon more classical Pavlovian discoveries and concepts. A conference on the Physiological Teaching of Academician I. P. Pavlov[22] held

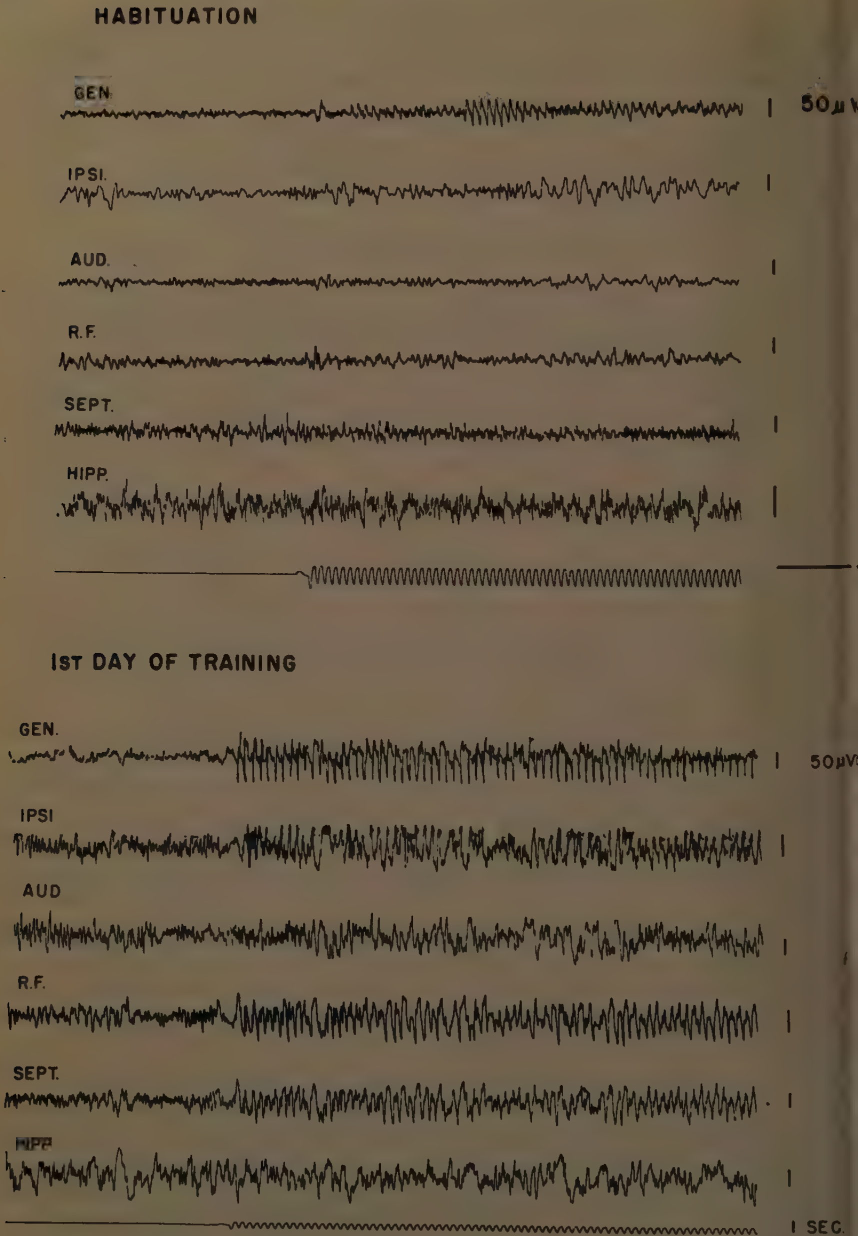

FIGURE 5. Records of electrical activity from cortical and subcortical regions of the cat brain, showing (*above*) the minimal and restricted response to repetitive photic stimulatio (signal) after habituation; and (*below*) the marked increase in amplitude and the widesprea generalization of responses when reinforcement is introduced.

The channels are, from the top: GEN, lateral geniculate body; IPSI, visual cortex; AUI auditory cortex; RF, midbrain tegmentum; SEPT, septum; and HIPP, hippocampus. Fro John and Killam;[14] reproduced by permission from *The Journal of Pharmacology and Exper mental Therapeutics.*

in Moscow in 1950 was influential in extending on many fronts the study of higher nervous activity that was inaugurated and developed so extensively by Pavlov and his associates after the turn of the century.

One of the most fruitful of the ensuing programs has studied the Pavlovian orienting or investigatory reflex, which forms an initial step in the establishment of conditional learning. The progress of this program has formed the subject of three annual conferences on the orienting reflex held in Kiev in 1958, 1959, and 1960. Some of the findings were also presented by Voronin and

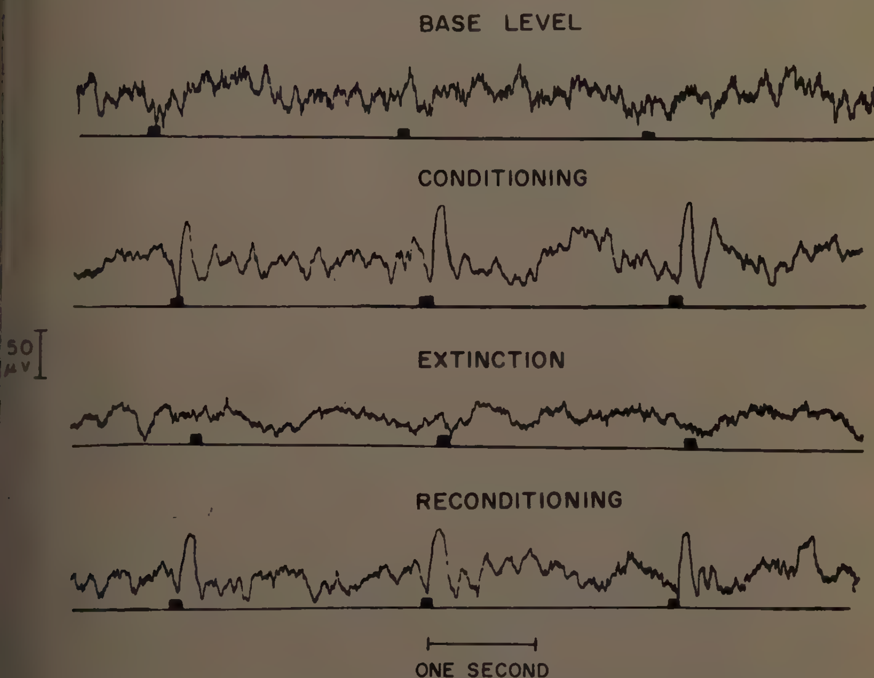

FIGURE 6. Records of electrical activity from the monkey's hippocampus, showing variations in the responses evoked by tone stimuli (signal). From the top the responses are: in the control period; during reinforcement with sugar pellets in conditioning; after extinction; and during subsequent reconditioning (with food reward again presented). From Hearst, Beer, Sheatz, and Galambos;[9] reproduced by permission from *Electroencephalography and Clinical Neurophysiology.*

Sokolov[27] at the Moscow Colloquium on Electroencephalography of Higher Nervous Activity (1958). Current status of the program was surveyed by Sokolov[26] at the Macy Conference on the Central Nervous System and Behavior in 1960. From these several sources and from the valuable recent reviews by Razran[23] and by John[13] the following synthesis and interpretation is attempted.

The orienting reflex differs from adaptive reflexes in a number of ways. Its important role in conditioning is seemingly related to induction of a central neural state described as alertness or attention. In addition to this singular feature, the orienting reflex is not specific to the modality of stimulation and its responses are initially generalized, although later they may become restricted

to a part of the body or to a region of the brain most closely related to th evocative stimulus. Furthermore, unlike specific reflexes, the orienting refle tends to habituate rapidly upon stereotyped repetition of stimulation.

While the orienting reflex is of initial importance for conditioning in evokin the functional state described as attention, after the conditional reflex has be come stabilized, an orienting reflex, induced once more by some novel stimulus can then provide a means by which the conditional response can be transientl reduced or prevented, by so-called external inhibition. In this situation, th action of the external inhibitor seems to involve both a redirection of attention and, from the work of Hernández-Peón and his associates,[10] a blocking of cen tral conduction of the conditional signal so as to prevent evocation of what under the circumstances, might be an inappropriate response.

The orienting reflex includes somatic, visceral, and EEG alterations, all o which tend to enhance the discriminatory power of the analyzers, enablin them to gain more information about the unusual properties of the evocativ stimulus and thus preparing the subject for dealing more effectively with it Movements of the eyes, head, or body may occur. There are usually change in respiration and heart rate. There is a vasodilatation of the head vessels, vasoconstriction of the finger vessels, and a galvanic skin response. There is generalized EEG arousal reaction, or blocking of the alpha rhythm by low voltage fast discharge. As Razran[23] has pointed out, unlike other reactio patterns of the organism those of the orienting reflex do not manage the initiat ing stimuli but are merely reactive to their presence. Orienting reaction pat terns are thus more preparatory than consumatory and are preadaptive rathe than adaptive in nature.

The aspect of novelty is the prepotent feature of stimuli evoking the orient ing reflex. This reflex's typical induction by nonstereotyped stimulation ha given rise to the concept that the orienting reflex is not initiated directly b the stimulus, in the customary sense of the term, but rather is induced by change in its modality, intensity, temporal pattern, or other parameter. A comparison of present with previous stimulation seems to be of major impor tance, with an orienting reflex being evoked at every point of disagreement i such comparison. This reflex is induced whenever new stimuli are discordant rather than accordant, with earlier stimulation.

The concept of a cortical neuronal model, it has been proposed, may accoun for this induction of the orienting reflex by stimuli whose characteristic featur is their nonstereotyped quality. This neuronal model is conceived as a ce assembly that preserves information about the modality, intensity, duration and order of presentation of earlier stimuli with which analogous aspects of th novel stimulation may be compared. According to the hypothesis, the orient ing reflex is evoked whenever, upon such comparison, the parameters of th novel stimulus do not coincide with those of the neuronal model. The orient ing reflex is considered the result, then, not of stimulation itself, but rather c impulses caused by the difference between such stimulation and the establishe model.

When properties of novel stimulation differ from those of the neuronal mode this discordance, it is suggested, may generate corticifugal discharge to th brain stem reticular system, the increased activity of which evokes the orien

ing reflex. In this scheme, therefore, cortical feedback to the reticular system is conceived as evoking the orienting reflex, and much more significance is attached to cortical influences upon the reticular formation than to the latter's more direct subcortical excitation.

In the contrasting situation, when novel stimuli are accordant with the proposed neuronal model, the cortex fails to excite the reticular system, and the orienting reflex is not induced. Moreover, upon repetition, such accordance of stimulus and model is proposed to generate inhibitory corticifugal discharge

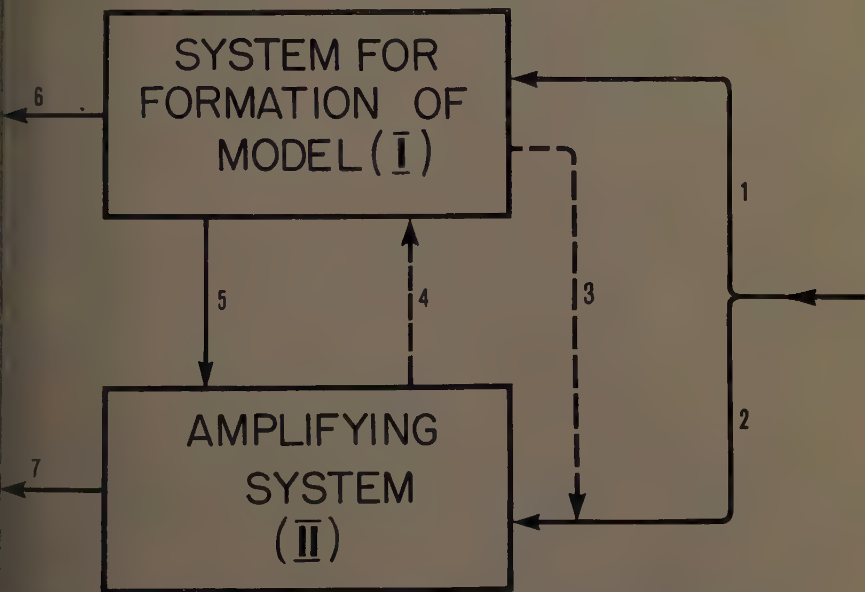

FIGURE 7. Schema of the brain mechanisms involved in the orienting reflex. I is the neuronal model; II is the amplifying system in the brain stem reticular formation.

The functional connections are: (1) specific pathway from receptor to cortical neuronal model; (2) collateral afferent path to reticular formation; (3) negative feedback from cortical model to afferent reticular collateral; (4) ascending reticular activiting pathway to cortex; (5) corticoreticular connections signalling con- or discordance between afferent stimuli and the cortical neuronal model; (6) corticifugal pathways for specific responses; and (7) reticulofugal pathways for nonspecific somatic and visceral responses. From Sokolov;[26] reproduced by permission from *The Central Nervous System and Behavior.*

to the brain stem, which blocks input to the reticular formation by way of collaterals from afferent paths and thus provides the basis for habituation. In this view, habituation is a consequence of inhibition at central afferent relays between peripheral receptors and the reticular formation, the inhibitory influences being corticifugal in derivation and generated by an accordance between novel stimulation and an established neuronal model.

Sokolov's hypothesis,[26] diagrammed in FIGURE 7, thus acknowledges the participation of subcortical mechanisms in the orienting reflex but proposes that they are managed and dominated by corticoreticular influences. It is suggested that these, in turn, are consequences of the comparison of novel stimuli with neuronal models established in the cortex by previous stimulation. Dis-

cordance between novel input and the model evokes excitatory corticoreticul:l discharge and triggers the orienting reflex. Accordance of input and mode not only fails to provoke an orienting reflex but additionally induces inhibitor corticoreticular influences responsible for habituation.

Although presented without specific reference to neural mechanisms, a r markably early expression of the concept of matching of novel with previo stimulation was given by Xavier Bichat in his *Physiological Research on Li and Death*, first published in 1800. Bichat's views seem so relevant to th present discussion that it may be appropriate to conclude with their quotation

"The action of the mind on each feeling of pain or pleasure, arising from sensation, consists in a comparison between that sensation and those which have preceded it. The greater the difference between the actual and pa impressions, the more ardent will be the feeling. That sensation would affe us most which we had never experienced before.

"It follows, therefore, that our sensations make a greater or less impressi upon us according to the frequency of their repetition, because the compariso becomes less sensible between their past and actual state. Every time that w see an object, hear a sound, or taste a dish, we find less difference between wha we experience and what we have experienced.

"The nature of pleasure and of pain is thus to destroy themselves, to cea to exist, because they have existed. The art of prolonging the duration of o enjoyments consists in varying their causes."

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INTEGRATION OF NEUROPHYSIOLOGICAL AND BEHAVIORAL RESEARCH

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I visited the Soviet Union in the spring of 1960, and the welcome received from my colleagues in the laboratories, from the Intourist Trave Bureau, and from the "man in the street" was everything that anyone coul wish. In view of the heart-warming hospitality that was extended to me i the Soviet Union, I take especial pleasure in being a contributor to this mono graph, which is the result of collaboration with our distinguished colleagues fron the Soviet Union. I reiterate the hope expressed by others in these pages tha we can build from the ground up a firm basis for understanding between th peoples of our two great nations. Modern science has the power to build better life for all the people in all nations of the world. It is imperative tha this vast power be used, not destructively, but creatively.

Magoun's talk has been a masterful summary of the field to which his ow work, his ideas, and his students have contributed so much. I shall begin b noting briefly how electrophysiological observations of the type he has describe run parallel to, and cast new light on, certain behavioral observations.

Variety of Responses Involved in Simple Conditioned Response

My first point is that it is becoming ever more clear that even such an ap parently simple thing as a conditioned reflex is actually a complex act of learn ing that involves many different activities in different parts of the organism

First, let us look at the behavioral evidence. From the very beginnin Pavlov (1927) emphasized that the salivary conditioned response (CR) involve much more than the response of that single gland. He called attention to th orienting response and other motoric components. One of our distinguishe colleagues, P. K. Anokhin (1959), has carried this point further in ingeniou experiments that show how this apparently simple type of learning involve complex biological adjustments of the entire organism. In one such exper ment he used a tone that always signalled meat in one dish, and a light tha signalled bread in a different dish. After discriminative CRs had been thor oughly learned, Anokhin put bread in the meat dish. This procedure produce obvious disruption in the CR. Instead of eating the bread, the dog looked fron dish to dish. From this experiment Anokhin concluded that the dog wa learning not only specific motor responses of going to the correct dish, but als responses anticipatory to afferent feedback from a specific type of food.

In another experiment, Anokhin had a dog stand on four tambours whil learning the defensive CR of withdrawing a leg to a conditioned stimulus (CS signalling electric shock. He found that the very first phase of this respons was a postural adjustment of the whole body that prepared the dog to be abl to make the response of lifting a single limb without losing balance. Some o the functional characteristics of this response suggested that it was more prim

tive than the response of leg lifting, which is usually all that is studied. It also seemed to be mediated by somewhat different areas of the brain. From yet other experiments we know that conditioning usually involves changes in the heart rate, changes in the electrical resistance of the skin, and various patterns of vasodilation and vasoconstriction.

The foregoing behavioral and peripheral observations are paralleled by the studies that Magoun has summarized, showing that central changes in activity can be recorded electrophysiologically from many different parts of the brain during the learning of the conditioned reflex and, indeed, that such changes shift from one part of the brain to another during different parts of the learning. Thus we see that the electrophysiological observations parallel the behavioral ones; both of these types of observations show that even a simple conditioned response typically is not a phenomenon isolated in one small part of the organism.

Danger of Overestimating Causal Significance of Responses Recorded in Brain

At this point I desire to interject a note of caution that will emphasize the importance of working out in point-for-point detail the relationships between neurophysiological and behavioral observations.

Since we all believe that the brain is the site of learning, we are likely to feel that, when we are recording from within the brain, we are getting directly at the heart of the learning process. It is possible that this feeling may sometimes mislead us. Some of the things that we record from the brain may not be crucial causal links in learning, but rather may be epiphenomena or, in other words, superficial phenomena that happen to be correlated with learning but are not essential for it.

For example, we have already seen that changes in the heart beat, electrical resistance of the skin, and the constriction or dilation of capillaries can occur with the establishment of the CR. However, when we are recording such peripheral events, we are not as strongly tempted to assign them a crucial role in the learning process. Some of the events we record directly from the brain may actually be as peripheral to the "connections" involved in learning as are the changes in heart rate and skin resistance. We must beware of a "halo effect" that can cause us to assign too much importance to events simply because they are recorded in the brain. Such a halo effect can prevent us from going on to establish the detailed relationships with behavior that are necessary to prove that these events actually play a crucial role in learning.*

Do not mistake my meaning. The techniques of directly stimulating and recording from the brains of normally behaving, unanesthetized animals represent an enormous advance in our possibilities for studying learning. However, it is necessary to follow through point by point, using carefully controlled experiments to establish the behavioral significance of each type of stimulation or recording.

* This cautionary point was first called to my attention by one of my former students, Warren W. Roberts, now at the University of Syracuse, Syracuse, N. Y.

Changes in Brain Activity Paralleling Phenomena of Generalization and Interference

Here it is appropriate to call attention to a second parallelism between phe-nomena revealed by neurophysiological recording, as summarized by Magoun and behavioral observations of learning. It is parallelisms of this kind that lead me to believe that the new neurophysiological observations are the be-ginning of an important breakthrough.

The classic work of Pavlov (1927) showed that, while a CR is being learned there is a phase of increasing stimulus generalization. Not only the origin CS, but other similar stimuli also, will evoke the CR. As the CR is thorough established and then given many additional training trials, however, the rang of stimulus generalization is narrowed down so that only stimuli more simil to the CS will elicit a CR. Similarly, Beritov (1924) in the Union of Sovi Socialist Republics and Culler *et al.* (1935) in the United States have observe a similar initial broadening and eventual constriction on the motor side. Dur-ing the early stage of learning the defense CR of lifting a paw to avoid electr shock, there is increasing motor generalization, so that the dog struggles wit all of his body. With additional training, the response slowly becomes muc more localized and precise, so that the dog neatly lifts a single paw althoug as may be remembered from Anokhin's work, there are postural adjustmen that enable him to lift the paw efficiently without losing his balance.

The records of activity from the brain, which Magoun outlined in his pape follow a similar course. First, there is a phase of spread, during which activi is recorded from widely separated points in the brain. After additional trai ing, there is a phase of concentration, during which the activities become mo precisely localized. The parallelism between these records and the behavior facts of early generalization and later differentiation is suggestive.

It is inviting to speculate that the mechanisms I have just been describi are the basis for the fact that, during the early stages, learning a novel activi requires most of one's attention. When one is first learning to drive a car, on cannot simultaneously carry on a conversation. However, when one becom a skilled driver, one can talk to the passengers while driving. Perhaps th highly learned habit does not generalize as widely and does not involve as muc of the brain; hence it has less chance to interfere with other activities. Sim larly, experimental studies of human verbal learning and of transfer of traini (McGeogh and Irion, 1952; Osgood, 1953) show that, up to a certain poin additional practice in one activity increases the amount of associative inte ference and retroactive inhibition exerted on other activities. However, wi still more learning, the picture is reversed so that there is less such interferenc

Role of Motivation (Excitation of Center for Unconditioned Reflex) in Conditioning

Early in his work, Pavlov (*op. cit.*, p. 31, 32) found that "In the hung animal, food naturally brings about a powerful unconditioned reflex, and th conditioned reflex develops quickly. But in a dog which has recently bee fed, the unconditioned stimulus has only a small effect, and alimentary cond tioned reflexes either are not formed at all, or are established very slowly

Thus alimentary CRs are dependent on the biologically important drive of hunger.

The effects of hunger, however, have not been studied as systematically as have those of many other variables that affect conditioned responses. For example, if a CS is associated with the presentation of food to an animal when it is not hungry, it is conceivable that a connection will be formed that cannot be observed until the latent CR is activated by subsequent hunger. In other words, is a drive necessary for the learning of a CR or only for its performance? This is the problem of latent learning (Tolman, 1932) that has been studied by other techniques with equivocal results, because it is difficult to get animals to expose themselves to the proper conditions for learning unless they are motivated (Spence, 1951). Pavlov's technique of the CR should be a good way to solve this problem, however.

Richard C. DeBold and I have performed an experiment* designed to separate the effects of drive on the learning of a CR from those on its performance. Rats had a fistula inserted through their snouts to the roofs of their mouths so that water could be injected whether they were thirsty or not. This same fistula was used for electrical recording of conditioned tongue licks.† During the first, or learning phase of the experiment, rats were given a total of 150 trials during which a flickering light was the signal for an injection of water into the mouth. All rats were on a schedule of 22 hours of water deprivation. Four experimental groups were run, with differing degrees of thirst achieved by the following treatments immediately before each day's training: (1) strong thirst with no drinking before training; (2) moderate thirst, allowed to drink before training 70 per cent of amount usually consumed; (3) satiated by drinking ad lib during 1 hour before training; and (4) supersatiated by normal satiation plus injection via the mouth fistula of an additional 70 per cent, most of which the rats allowed to drool out of the mouth. As a control for general level of licking and for pseudo-conditioning, 4 similar control groups were run with exposure to the same number of lights and injections that never were paired with each other. Conditioning was measured by the difference between each experimental group and its control group.

During training the strong thirst group showed a typical negatively accelerated learning curve of conditioning and the moderate thirst group showed a similar but lower learning curve of conditioning, while both of the satiated groups showed no conditioning.

During the testing phase of the experiment one half of the rats in each group were given 5 trials of exposure to the lights alone when they were 22 hours thirsty; the other half were tested following normal satiation. None of the groups tested, when satiated, showed any performance of the CR. Even when made thirsty neither of the groups that had been satiated during training showed any performance of the CR. On each test trial the group trained with moderate thirst averaged approximately 7 licks, and the one trained with strong thirst averaged 13. All differences were statistically highly reliable. In short,

* The experiments described here were supported in part by Research Grant M647 from the National Institute of Mental Health, Public Health Service, Bethesda, Md.

† Donald D. Jensen helped to develop this fistula in the Psychology laboratories of Yale University, and first observed conditioned tongue licks with it.

the drive of thirst was essential to both the learning and the performance o the CR.

In addition to the degree of hunger, alimentary conditioned responses ar dependent on another motivational variable, namely, the amount and qualit of food used as the unconditioned stimulus (US). In classic conditioning th CR is similar to the UR that is elicited by the US. In other situations, how ever, food may serve to reinforce the learning of responses that are completel different from those it originally elicited. This kind of learning, which w shall call instrumental, has been extensively studied by Thorndike (1898 Miller and Konorski (1928), Skinner (1938), Hull (1943), Spence (1956), an many others.

The strength of drive and the amount and quality of reward are importan also in these studies of instrumental learning. Futhermore, such studies hav emphasized the importance of the schedule or, to state it more generally, th terms of reward (Logan, 1960). The foregoing motivational variables hav been studied in considerable detail in experiments on instrumental learnin They have not yet been studied in as much detail in experiments on class conditioning.

Are Visceral Responses Subject to Instrumental Learning?

The somatic nervous system, running medially through the spinal cord, an the autonomic nervous system, running laterally through a chain of gangli have been considered two main divisions of the nervous system. We kno that responses of the skeletal muscles innervated by the somatic nervous sy tem and, also, the visceral responses of glands and smooth muscles innervate by the automatic nervous system, are subject to classic conditioning. Wo in the Soviet Union (Bykov, 1957) has shown how many different viscer responses can be conditioned.

We know that responses of the skeletal muscles innervated by the somat nervous system are subject to instrumental learning. Many people (Schlo berg, 1937; Skinner, 1938; Mowrer, 1950) believe, however, that visceral r sponses innervated by the autonomic nervous system are not subject to instru mental learning. If so, this is an extremely important difference between the two parts of the nervous system.

It seems to me, however, entirely possible that this apparent dichotomy not the result of a basic difference in the fundamental properties of these tw branches of the nervous system but, instead, is the result of the way in whic the effectors of these systems are related to the environment under the norm conditions of life. Since the smooth muscles and glands usually do not hav any instrumental effect on changing the external environment, instrument responses of this kind have not been previously reinforced. Therefore labor tory experiments on such learning not only require special instrumentation, bu they also may start without the advantage of the enormous amount of transf of training that usually is available to help the instrumental learning of tho somatic responses usually selected for experimental study.

I believe it is important to direct research toward this neglected problem order to find out whether these two branches of the nervous system obey diffe ent laws. If they obey the same laws, a dog rewarded whenever he salivat

strongly should secrete more saliva than one given the same average number of rewards at times when he is salivating the least. Initially it might be convenient to use hunger as the drive and a liquid food as the reward, but it should be possible to transfer the response by stages to thirst as the drive and pure water as the reward. Indeed it should be possible with enough patience to learn the response from the beginning under the latter condition. Similarly, it would be interesting to see whether other visceral responses that have been conditioned, such as changes in heart rate and vasoconstriction or vasodilation, are subject to instrumental learning. Such learning would have obvious implications for psychosomatic symptoms, extending into this new realm the type of learning-theory analyses of neurotic symptoms and psychotherapy made by Dollard and Miller (1950). Whichever way such sufficiently intensive studies turned out, the results would increase our basic understanding of mechanisms of learning and the functions of the nervous system.

Can Activity in Sensory Areas of the Brain Show Instrumental Learning with Suitable Reward?

Magoun has summarized studies indicating that the process of classic conditioning applies not only to areas of the brain controlling motor and visceral responses that can be recorded peripherally, but also to activities in sensory areas of the brain that could not very well be directly studied objectively without the technique of electrophysiological recording. Such purely sensory conditioning usually is somewhat variable and transient. Perhaps such responses would become more stable and permanent if they were specifically rewarded. For example, one could expose a hungry animal to a light as the signal for a series of clicks followed by food. If one recorded anticipatory "evoked potentials" from the auditory area, one might reward these by food. If this is successful, one might gradually omit the clicks, making the reward of food dependent upon the appearance of a pattern of activity in the sensory cortex closely resembling that originally evoked by the clicks. Can the activity of cells in the sensory cortex be controlled by rewards, or is instrumental learning possible only in the motor cortex? The answer to this question has basic implications for theories of learning. It is also relevant to problems of imagery and hallucinations.

If the foregoing line of research is indeed successful, the behavioral significance of the electrically recorded activity in sensory areas should be validated by rigorous tests. For example, suppose one has used a fixed-interval schedule to train a dog so that, whenever a light is on, the sensory cortex will periodically show activity similar to the evoked potential elicited by a series of clicks. After this, with the light off, the clicks themselves should be made the CS for a specific CR. Then, when the light is on and without any clicks, will the animal tend to show this CR whenever recording from the auditory cortex shows activity resembling the original evoked potentials?

Behavioral Significance of Direct Stimulation of Feeding Area of Brain

As a further illustration of integration between neurophysiological and behavioral approaches, I shall briefly summarize the results of a series of studies

on hunger elicited by direct electrical and chemical stimulation of the brai (Miller, 1957, 1960, 1961). Edgar E. Coons helped with this work.

Electrical stimulation of the lateral, so-called feeding area of the hypothala mus will cause thoroughly satiated rats to eat, but it will also cause them t gnaw inedible objects, such as sticks. How can one determine whether th electrical stimulation of the brain (ESB) is merely eliciting a reflex gnawin response or whether it has all of the functional properties of normal hunger In the first test we trained hungry rats to press a bar to secure pellets of foo Then we thoroughly satiated them until they stopped pressing the bar. W found that ESB in the feeding area caused them to perform the learned respons of pressing the bar to get food.

Perhaps, however, the ESB merely activates the somnolent, satiated ra which then performs the dominant habit in the situation, namely, pressing th bar. How can we eliminate this possibility? We used rats that were com pletely satiated on food but moderately thirsty, so that they were drinking a a water spout that projected into the apparatus. If ESB merely activate rats, it should have caused them to drink faster because this is the domina response. If it has the functional properties of hunger, however, it shoul cause the rats to leave the water spout to perform the habit that had bee reinforced by food. That is exactly what the ESB made these rats do.

Perhaps the ESB merely elicits reflex gnawing after all and, being compelle to gnaw, the rat would rather bite food than the walls of the apparatus. W eliminated this possibility by using a feeding response that did not involv gnawing. We found that satiated rats that could not be made to lap up plai water by ESB would lap up either sugar-water or milk. This experime showed that the response to the ESB was not primarily defined by a specifi set of movements, such as biting or lapping, but rather by the sensory feedbac of the taste of food.

Finally, we showed that satiated rats stimulated by ESB in the hunger are would learn to choose the side of a T-maze where such stimulation was turne off. In this respect, they were similar to normally hungry animals, which wi learn to choose the side of the T-maze containing the food that reduces the hunger. Since the termination of ESB in the hunger area serves as a rewar we certainly would not expect its onset to serve as a reward. Having learne that in this new area of investigation it is dangerous to leave any possibilit untested, however, we performed the experiment and found that rats woul learn to press a bar that turned on electrical stimulation to this area of th brain. In fact, rats will learn to press one bar to turn on the ESB in this are and another to turn if off. Since this dual reward-aversion effect can be se cured from other adjacent areas that do not elicit eating, either one or both o these effects may be an artifact of the spread electrical stimulation, rather tha a specific function of the feeding area. Although we must suspend interpreta tion of these last results, we have demonstrated an impressive parallelism be tween the behavioral effects of electrical stimulation of the "feeding" area o the brain and those of normal hunger.

Finally, a student in our laboratory (Grossman, 1960) has shown that stimu lation of the same area of the brain with minute amounts of the adrenergi substances, adrenaline or noradrenaline, will cause satiated rats to eat and als

to perform a learned response rewarded by food. By contrast, stimulation of the same area via the same cannula with minute amounts of the cholinergic substances, acetylcholine or carbachol, will cause satiated rats to drink and also to perform learned responses rewarded by water. Furthermore, the adrenergic stimulation interferes somewhat with the consumption of water by normally thirsty animals that have only water available, while cholinergic stimulation interferes with eating by hungry animals exposed only to food. Various control tests with other substances seem to rule out *p*H, vasoconstriction or vasodilation, and osmotic pressure as the primary sources of these effects. Finally, the foregoing effects can be eliminated by systemic administration of appropriate adrenergic or cholinergic blocking agents.

An earlier series of studies in the Yale laboratories (Miller, 1953; Delgado *et al.*, 1954) showed that the electrical stimulation of other parts of the brain has a number of the functional properties of normal pain and fear. Shortly thereafter, Olds and Milner (1954) discovered that electrical stimulation of still other areas could serve as a reward. Olds (1958) has followed up this striking discovery with an impressive series of studies showing that reward effects elicited by ESB can have a large number of the behavioral properties of normal rewards.

We have seen how the techniques of electrical and chemical stimulation are yielding basic information on drive and reward. It is to be hoped that additional progress can be made by more extensive application to this problem of the additional techniques of electrophysiological recording, electrolytic lesions, and introceptive conditioning as used, for example, by Airapetjantz (1956).

Arousal, Orienting Reflex, and Exploratory Drive

Returning to the work of Magoun (1958): we are all familiar with the arousal response. This has been studied primarily by modern electrophysiological techniques. Brilliant recent work by Sokolov (1958) indicates that the arousal response is part of the same pattern that Pavlov (1927) originally identified as the orienting reflex. Both the peripheral orienting and central arousal components of this pattern are aroused by novel stimuli and ordinarily are subject to fairly rapid habituation whenever the same stimulus is repeated in reasonably massed trials.

It does not take an enormous leap of the imagination to connect the phenomenon of arousal and the orienting reflex with those that psychologists in the United States (Berlyne, 1950; Harlow, 1953; Montgomery, 1953; and Myers and Miller, 1954) have studied under the names of curiosity or exploratory drive. In the foregoing studies I particularly desire to call attention to the fact that curiosity can function as a motivation to produce learning and to maintain performance. For the bored animal, the appearance of a novel stimulus functions as a reward. This fact may be the basis for the learning that appeared in the experiments on sensory conditioning cited in his paper by Magoun. Perhaps the novelty of the stimuli served as the reward for that learning. Perhaps the transience of such sensory CRs is the result of habituation to novelty, which removes it as a source of reward.

Conceivably, a similar factor of novelty serves as a reward for the motor CRs that Doty and Giurgea (1961) have been able to establish by pairing electrical

stimulation in a sensory area with electrical stimulation of the motor corte while Loucks (1935) failed to get such conditioning without an added rewar If so, habituation of the effect of novelty (orienting reflex and arousal) migh be the reason why these experimenters fail to get any CRs if the trials are no distributed widely.

The foregoing speculation could be checked by recording the traditional sig of arousal and orientation as well as CRs in experiments with trials present at different rates. At the same time, a direct test should be made to s whether the stimulation employed in these experiments can function as a r ward in instrumental learning. While Doty and Giurgea report impressi data indicating that the direct stimulation of the brain used in their expe ments did not have any strong aversive effect, they have not investigated thoroughly the possibility of a rewarding effect.

A technique developed in our laboratory might be used to investigate po sible rewarding effects of stimuli involved in experiments on conditioning th do not seem to involve obvious motivation. First, hungry animals are train to press a bar for food. Then the apparatus is set so that the bar is disco nected from the reward mechanism most of the time and only the first bar pre after unpredictable intervals will be rewarded. This is called a variable-inte val schedule. The intervals are made long enough so that the animal w press the bar at a slow rate. In the test for rewarding or aversive effect stimulation, the bar is arranged so that every fourth press will deliver th stimulation. If the stimulation is rewarding, the animal will speed up; if it punishing, the animal will slow down. Fifteen-minute periods of stimulati are alternated with 15 min. periods without stimulation.

When ESB or peripheral stimulation has no obvious distracting motor sid effects, every bar press can be allowed to produce them; if the distracti effects are prolonged, the ratio of bar presses to ESB can be increased.

In view of the possibility of either the reward effect described by Olds (195 or a novelty effect of the type discussed, I believe that some test similar to th one just described is essential before concluding that conditioning is occurri without any motivation. Combining such careful behavioral tests with th powerful new neurophysiological techniques will greatly increase our knowledg of the brain mechanisms responsible for learning.

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MORPHOPHYSIOLOGICAL BASIS OF ELEMENTARY EVOKED RESPONSE PATTERNS IN THE NEOCORTEX OF THE NEWBORN CAT*

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It has often been inferred, when not overtly stated, that the continued em ployment of modern electrophysiological techniques in behavioral studi should provide valuable information that will permit formulation of a gener neurophysiological theory of adaptive behavior. This assumption involv at least three additional suppositions: (1) that the different varieties of electr physiological data obtainable in behavioral experiments are analyzable terms of the properties of different neuronal organizations; (2) that these pro erties are sufficiently known to warrant attempts at their analysis; and (that the data are relevant to the neurophysiological processes subservi learning. Neglecting any consideration of the validity of these assumption it may be profitable to examine some of the problems they encompass. On of these is the problem of defining more precisely the nature of some of th sustained electrophysiological changes recorded in different neuronal organiz tions during different phases of conditioning and habituation.[1] Closely r lated to this is the problem of attempting to specify the morphophysiologic characteristics of the synaptic organizations involved in elaborating the alterations. The extraordinary complexity of these problems cannot be ove emphasized; nor, for that matter, can we overemphasize the advantages th may result from utilizing a variety of operational methods to achieve the solution.

In the present report one analytical approach is described that affords a opportunity for studying several aspects of the aforementioned problem This approach takes advantage of the distinctive properties of cortical sy aptic organizations in the newborn cat to provide data relevant to the follow ing questions: What morphological features of cortical organization in th newborn animal can provide significant clues to the nature and origin of diffe ent electrocortical activities? Can cortical synaptic organizations elabora complex electrocortical events prior to the development of organized "spo taneous" activity? Are there differences in the degree to which differe synaptic organizations participate in these events? Although an attempt made here to supply tentative answers to these questions, it is clearly reco nized at the outset that the present effort is inadequate for the task. We this not the case, it might be inferred that the complexities of the cerebr cortex could be unraveled with greater facility in the immature than th mature animal. Suffice it to say that this fiction need not be seriously ente tained.

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A Note on the Preparation of Neonatal Kittens

The electrophysiological data summarized below were obtained in perinatal ittens (< 3 days old) born in the laboratory. Records shown in FIGURE 1 eft) were from experiments on a near-term fetus delivered by caeserean section. All experiments were performed on locally anesthetized, succinylcholine-aralyzed kittens initially prepared under general (ether) anesthesia.[2,3] Emhasis was placed on the necessity for avoiding excessive blood loss in the reparation of newborn animals, as well as avoiding the depressant effects of arbiturates. In a number of instances some of the complex electrocortical vents described below in 1- to 2-day old kittens were either not obtainable or f a transient nature. Failure to demonstrate these events was generally ttributable to the traumatic effects of cerebellectomy or other procedures mployed to expose brain stem and cerebrum for stimulation. In some "de-

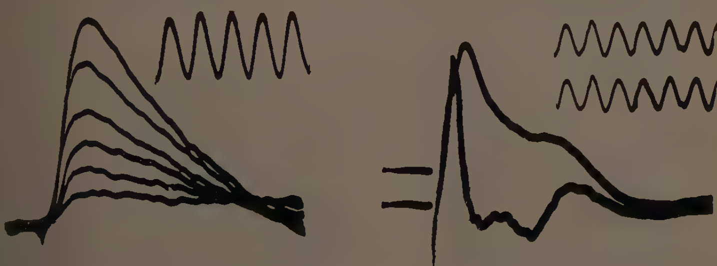


FIGURE 1. Characteristics of long-duration superficial cortical responses (SCR) recorded .5 mm. from the stimulating electrodes on the suprasylvian gyrus in a near-term fetal kitten *eft*). The stimulus frequency was 0.5/sec., and six superposed responses at different stimulus rengths are shown. Negativity is at the top in this and in all subsequent figures.
Right: A five-hour-old kitten. Comparison of the SCR recorded at 0.5 mm. with a large 0.5 mm.) ball-tipped electrode (*upper channel*) and the SCR recorded "at the site of stimulaion" with a 0.1 mm. wire electrode. When recorded with the wire electrode at the site of timulation, the SCR has characteristics identical to those recorded in the adult animal.[2] alibration: 100 cps; 0.1 mv.

eriorating" preparations, especially those with brain stem exposures, 1 to 2 c. transfusions of packed red cells obtained from adult cats generally produced ramatic recovery of excitability.

Stimulation of subcortical structures in 1- to 2-day old kittens was accomlished with 0.5 mm. concentrically bipolar electrodes held in three-coordinate anipulators. Other details of the stimulating and recording techniques deribed here were similar to those noted elsewhere.[2-5]

orphophysiological Features of Superficial Neocortical Neuropil in Newborn Cat

The fact that apical dendrites of cortical pyramidal neurons are extraordiarily well developed at birth in the cat[2,6] is one of several reasons for focusing n the immediate neonatal period in the present analysis. Others are reealed by examination of the characteristics of pyramidal neurons at various ages in their postnatal morphogenesis (FIGURE 2). The significant structural atures of these elements in the newborn cat are the vertically oriented apical endrites that extend into the molecular layer, the absence of axon collaterals

FIGURE 2. Maturational changes in neocortical pyramidal neurons during postna ontogenesis (Golgi-Cox preparations; microphotographs taken from 200 μ sections). *a:* Fi hour-old kitten. The central cluster of medium pyramidal neurons shows elements w prominent apical dendrites extending into the molecular layer. The tangential branches the apical dendrites are absent, the basilar dendrites are poorly developed, and the axon col erals are insignificant at this stage. ×95. *b:* An eight-day-old kitten. The medium pyra idal neuron shows minimal tangential branches on the proximal segment of the apical d drite. The basilar dentrites begin their maximal rate of growth during this period. One s dendrite, several times the cell body diameter in length, is shown extending to the left. ×1 *c:* A 14-day-old kitten. The pyramidal neurons have well-developed basilar dendrites a tangential branches on their proximal apical dendritic segments. The dendritic spines prominent at this time. The deep neuropil is undergoing the final phase of elaborati ×150. *d:* A 21-day-old kitten. The dendrites of all elements have completed their maxim rates of expansion. The extraordinary complexity of the deep neuropil is due to profou growth of the basilar dendrites of the pyramidal neurons and axon collaterals. The ap dendrites and their deep tangential branches increase in length up to this stage. The tang tial branches of the apical dendrites in the molecular layer do not exceed 100 to 200 μ.[6] ×1

and tangential branches of apical dendrites, and the poor development of basilar dendrites. The last feature is important with respect to the analysis of evoked potentials in neonatal cortex presented below.

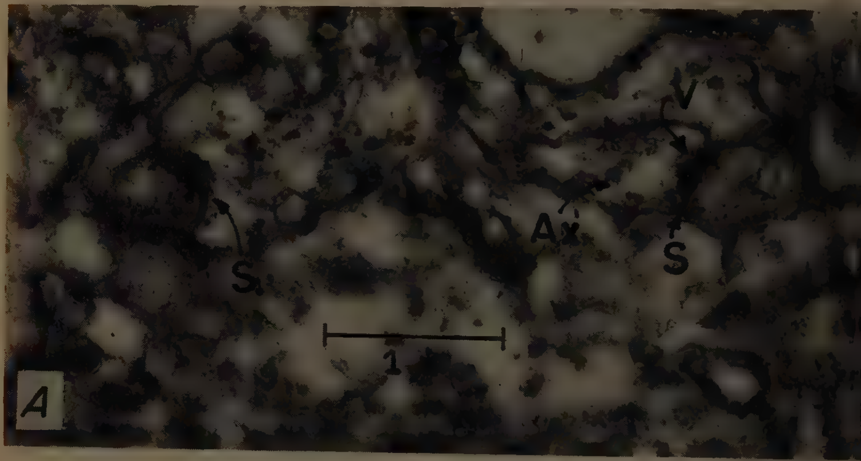
For our present purposes it is sufficient to note that the analysis of axodendritic synaptic organizations after the first postnatal week can be expected to be complicated by the extraordinarily rapid development of synaptic organizations involving basilar dendrites (FIGURE 2*a*). The latter attain their maximum rate of expansion during the second postnatal week (FIGURE 2*b*) and, by the end of the third postnatal week, have virtually reached a stage of final maturation (FIGURE 2*d*). During this period of basilar dendritic and axon-collateral proliferation, proximal segments of apical dendrites develop tangential branches, but tangential spread of apical dendrites in the molecular layer rarely exceeds 200 μ even in the mature cat cortex.[7]

In addition to apical dendrites of pyramidal neurons and dendrites of superficial stellate cells, the molecular layer of neonatal cat neocortex contains numerous Cajal-Retzius cells.[2,6] These elements, which in the cat appear to undergo "regressive" changes after the first postnatal week, provide horizontal axons and additional dendritic surfaces for synaptic contacts in superficial neuropil. Ascending axons terminate at all levels in neonatal cortex. Relatively large numbers of these are closely associated with apical dendrites throughout their entire course.

The picture that emerges from examination of suitable Golgi-Cox material provides a satisfactory basis for the assumption that synaptic activities evoked in the neocortex of the newborn cat are predominantly generated in apical dendrites of pyramidal neurons.[2] This hypothesis is strongly supported by recent observations on the ultrastructure and distribution of synapses in neonatal cat neocortex. Electron microscopic studies carried out by K. Voeller in collaboration with G. Pappas and myself,[8] reveal large numbers of axodendritic synapses in the superficial neocortical neuropil of the newborn cat (FIGURE 3). These appear to be identical in all respects to those described in the cerebral cortex of the adult rat.[9] Although both Type I and Type II axodendritic synapses have been observed in neonatal cat cortex, synaptic complexes involving dendritic spines[9] have not been observed in the newborn animal. This is not surprising, since available data from Golgi-Cox material indicate that dendritic spines or thorns are not prominent until the end of the first postnatal week[6] (FIGURE 2*b*). These spines are, however, well developed by the end of the second week (FIGURE 2*c*). The significance of the absence of dendritic spines and their synapses in the first postnatal week remains to be elucidated. Of particular significance is the failure, as yet, to detect axosomatic synaptic complexes in the immediate perinatal period. Although this suggests that relatively few axosomatic synapses are present on neocortical pyramidal neurons in the newborn cat, further speculation must be deferred until considerably more material has been studied.

The foregoing light and electron microscopic data indicate that superficial axodendritic synaptic organizations have attained a high degree of morphological differentiation in the newborn cat. Additional support for this has been forthcoming from electrophysiological studies on superficial cortical responses (SCR) evoked by cortical surface stimulation.[2] SCRs recorded close

to the site of stimulation have electrographic characteristics identical to thos recorded in adult animals.[4,10,11] The relatively long duration of SCRs evoke at more distant sites is attributable to summation of "unit" 12 to 20 mse postsynaptic potentials (p.s.p.s), generated in superficial dendritic element by conductile pathways of varying trajectory. One major difference in th composition of superficial axodendritic pathways involved in SCRs evoked i



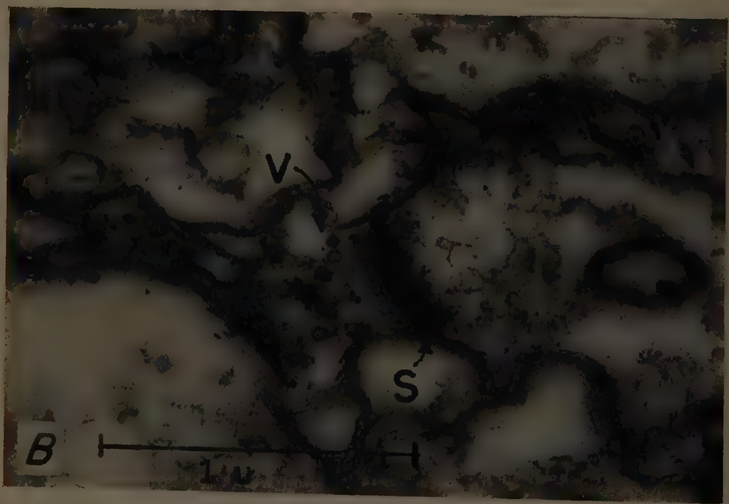


FIGURE 3. Electron micrographs of the axodendritic synaptic complexes in the superficia neocortical neuropil of the newborn cat.

A. Two synapses (S) are shown at arrows. The axon (Ax) is readily identified by th presence of synaptic vesicles (V), some of which are concentrated at the presynaptic mem brane. ×25,000.

B. Higher magnification of another axodendritic synaptic complex to show details of th synaptic vesicles and the characteristics of thickened synaptic membranes.[8] ×43,500.

newborn and mature animals is worthy of note. In adult animals, SCRs are rapidly augmented following topical application of long chain "convulsant" ω-amino aliphatic carboxylic acids,[5] whereas such augmentation is not observed in immature cortex SCRs until the third postnatal week.[12,13] If, as has been proposed elsewhere,[5,14,15] long chain ω-amino acids produce changes in evoked cortical responses by elimination of inhibitory axodendritic p.s.p.s, then it is not unreasonable to suspect that the lack of pharmacological responsiveness to these compounds is associated with the absence of a significant component of axodendritic inhibitory p.s.p.s in the SCR evoked in the neonatal cat cortex. Mention is made of this ontogenetic difference in the pharmacological properties of some superficial axodendritic pathways to emphasize the potential value of specifically acting pharmacological agents in studying the ontogenesis of functionally different cortical synaptic organizations.[13]

Characteristics of Axodendritic Activities in Specific and Nonspecific Projection Cortex During the Neonatal Period

One reflection of the selective differentiation of superficial axodendritic synaptic pathways in the neonatal cat cortex is seen in the electrographic characteristics of specific evoked responses to stimulation of ventrolateral thalamic nuclei and their projections (FIGURE 4). Such responses evolve with little initial surface positivity and are prominent surface-negative responses,[16] unlike those ordinarily recorded in the somesthetic projection cortex of mature animals.[17] Since the initial surface positivity of specific evoked responses represents largely a reflection of subsurface depolarizing p.s.p.s,[18] its relative absence might be construed as a sign that synaptic activation of elements in cortical depths did not occur in the immediate neonatal period. That this is not the case has been shown by the finding that gamma-aminobutyric acid (GABA)-elimination of surface negativity in the neonatal cortex specific responses unmasks a small surface positivity attributable to subsurface depolarizing p.s.p.s.[13,19] Thus the singular characteristics of specific evoked responses in the neonatal period would appear to be due to the swamping of initial weak surface positivity by axodendritic p.s.p.s in superficial neuropil.

Despite the prominence of superficial axodendritic depolarizing p.s.p.s in primary evoked responses in the somesthetic cortex, synaptic pathways involved in the production of surface negativity in these responses exhibit prolonged postactivation depression in the neonatal period. Almost complete blockade of cortically evoked responses is seen following 10/sec. stimulation of the lateral thalamus (FIGURE 4) or 2 to 5/sec. contralateral forelimb stimulation.[16] Strong stimulation of anterolateral thalamic regions in newborn cats may evoke primary (surface-negative) responses in the posterior sigmoid (somesthetic) cortex and surface-positive responses in more widespread areas, including the anterior suprasylvian gyrus (association cortex), as shown in FIGURE 5. The latter responses are followed by long-latency surface negativity that increases in magnitude and decreases in latency during 5/sec. stimulation. With continued stimulation at higher frequencies (10/sec.), specific evoked responses are obliterated, and the early positivity in the suprasylvian cortex is followed by a prominent surface negativity that disappears at still

higher stimulus frequencies (25/sec.). Of particular interest is the differenc in the alterations seen after prolonged repetitive stimulation (FIGURE 5i–p). The recovery of both types of responses is followed by selective potentiation of the longer-latency negativity in the association cortex. Similar facilitation of long-latency surface negativity in the association cortex is demonstrabl during early phases of activity cycles initiated by paired conditioning-testin stimuli (FIGURE 6). The data indicate that whereas single shock stimulation

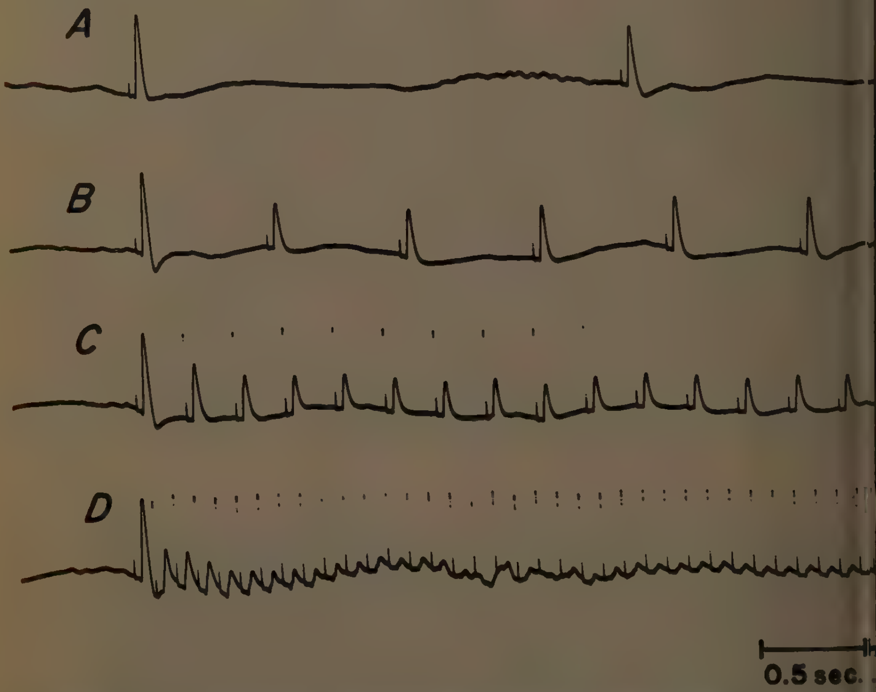


FIGURE 4. The predominantly surface-negative specific responses evoked in the posteri sigmoid gyrus following stimulation of the ventrolateral thalamic nuclei and their projection in an eight-hour-old kitten. The stimulus frequency was: *A*, 0.5/sec.; *B*, 2/sec.; *C*, 5/sec.; an *D*, 10/sec. A depression of responsiveness is evident during the 0.5/sec. stimulation and profound during the 10/sec. stimulation. Note the increased duration of surface-negativit in the second to the fifth responses in *D*, and the tendency for these responses to exhibit in tially rapid and later slow components prior to the almost complete blockade.

of anterolateral thalamic regions evokes activity that is followed by a rela tively prolonged phase of depression in superficial dendritic organizations i the specific projection cortex, the same stimulus initiates a phase of augmente excitability in superficial axodendritic organizations in the association corte that develops within a few milliseconds after stimulation and persists for we over 200 msec.

Involvement of axodendritic synaptic pathways in the production of po tentiated responses recorded from the suprasylvian gyrus of the neonatal ca cortex is shown by the finding that long-latency surface negativity in suc responses is generated in elements subtending almost the entire thickness

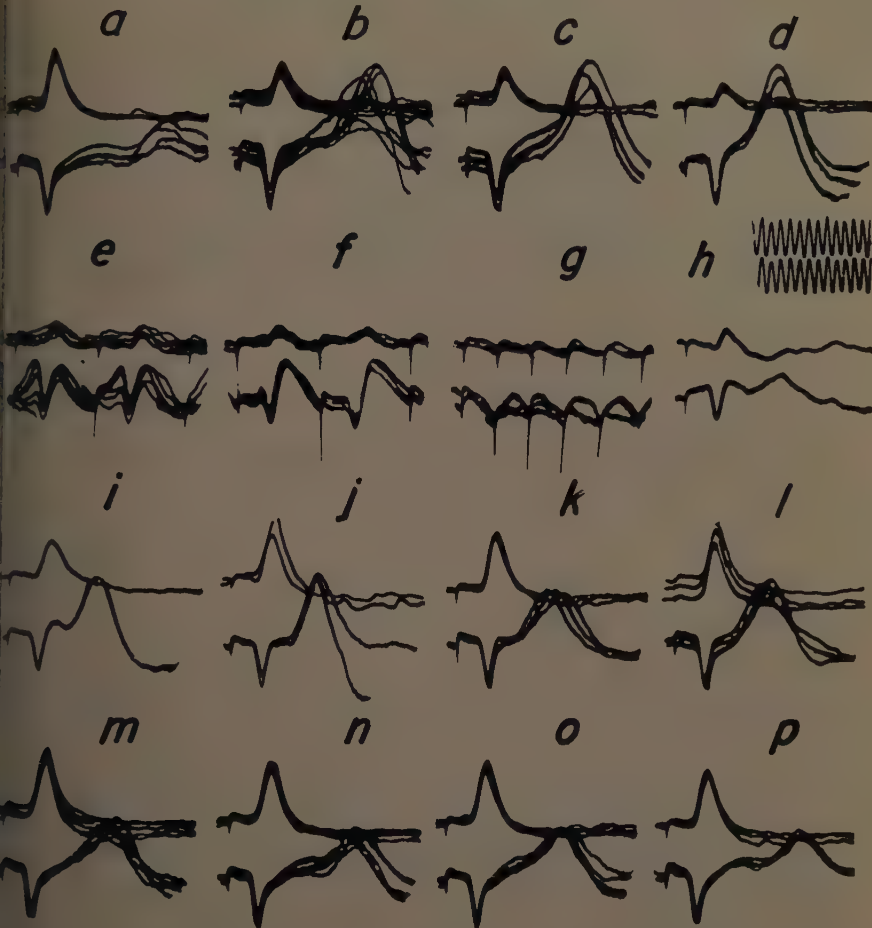


FIGURE 5. Responses evoked in the posterior sigmoid gyrus (*upper channel*) and the ante-
ior suprasylvian gyrus (*lower channel*) by stimulation of the anterolateral thalamus in a two-
lay-old kitten. *a:* Stimulation is 0.5/sec. The surface-negative response in the specific pro-
ection cortex is associated with a shorter duration surface-positive response in the nonspecific
ortex. A long-latency (120 msec.), variable surface-negative response in the anterior supra-
ylvian gyrus is barely detectable at 0.5/sec. stimulation. During the 5/sec. stimulation
b, c, d), the specific evoked responses are depressed, whereas the surface-positive component
ı the nonspecific cortex is unaffected. The succeeding negativity is markedly augmented in
mplitude and develops with a shorter latency (60 msec.). With 10/sec. stimulation (*e, f*),
epression of the specific responses deepens, and responses evoked in the anterior suprasylvian
yrus exhibit further changes consisting of abolition of late negativity and conversion of the
rior surface-positivity into a diphasic positive-negative sequence. Stimulation at 25/sec.
liminates all components except a small positivity in the anterior suprasylvian gyrus (*g*).
'ollowing this, the responses evoked by stimulation at 0.5/sec. (*h* to *p*) show an initial 2- to 4-
ec. phase of depression. After recovery of specific responses, facilitation of the long-latency
urface-negativity in the nonspecific cortex persists for more than 2 min. The superposed
sponses in *m* to *p* are samples of a continuous series of records during the 2-min. period of
ostactivation facilitation. Calibration: 100 cps; 0.1 mv.

the neonatal cortex (FIGURE 7A). Extracellularly located micropipettes intro-duced from the surface (a) to a depth of 0.6 mm. (b), record little change i focal negativity evoked by anterolateral thalamic stimulation, whereas prio positivity is markedly attenuated. During c and after d to h repetitive stimu-lation, no change is detectable in the early components of focally recorde responses, but the intracortical slow negativity undergoes changes that occu independently of alterations in surface negativity. This dissociation betwee surface and intracortically recorded focal negativity is further demonstrate by the effects produced by systemically administered GABA in neonatal prepa-rations, in which prolonged cortical exposure has resulted in changes in th

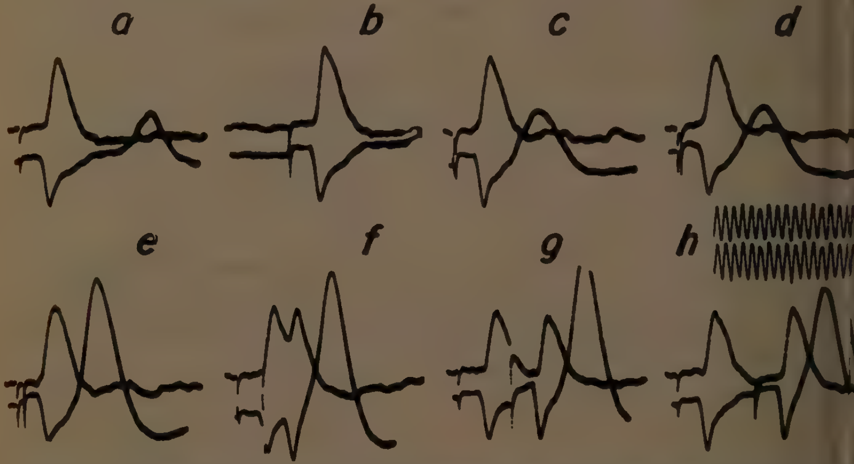


FIGURE 6. The activity cycles of evoked responses, similar to those shown in FIGURE 5 bu recorded at an earlier time in the same experiment. *a* represents the conditioning response *b* is the testing responses; and *c* to *h* represent the responses evoked every 2 sec. by pairs stimuli with progressively increasing intervals. With stimulus intervals of 2 to 10 msec conditioning responses are unaffected, but testing responses in the specific cortex are complete blocked. The long-latency surface-negativity of the conditioning response in the nonspecif cortex is markedly facilitated with short-interval paired stimuli. Selective facilitation long-latency surface-negativity in the testing responses in the anterior suprasylvian gyru persists for nearly 200 msec. Note the insignificant effect of long-interval paired stimu on the prior positivity in the anterior suprasylvian gyrus. Calibration: 100 cps; 0.1 mv.

blood-brain barrier permeability to the ω-amino acid.[19] In the experimen illustrated in FIGURE 7B, strong thalamic stimulation evoked responses wit prominent long-latency surface negativity in the anterior suprasylvian gyru Intracortical responses consisted of an initial short-latency negativity and sub-sequent low-amplitude positivity (FIGURE 7Ba). During the period of pos activation facilitation of surface negativity, long-latency negativity was al recorded from the cortical depths FIGURE 7Bb). Systemic GABA selectivel eliminated the long-latency surface negativity. During the action of GABA long-latency positivity appeared only in surface recordings in the postactiva-tion period, whereas intracortical negativity was still recorded as in the pos activation period prior to GABA injection. Although these data lend them-selves to a number of interpretations, a reasonable assumption is that th

urface and intracortical negativities evoked in the nonspecific projection ortex are summated focal excitatory p.s.p.s independently generated at varius loci along vertically oriented apical dendrites, since the latter elements

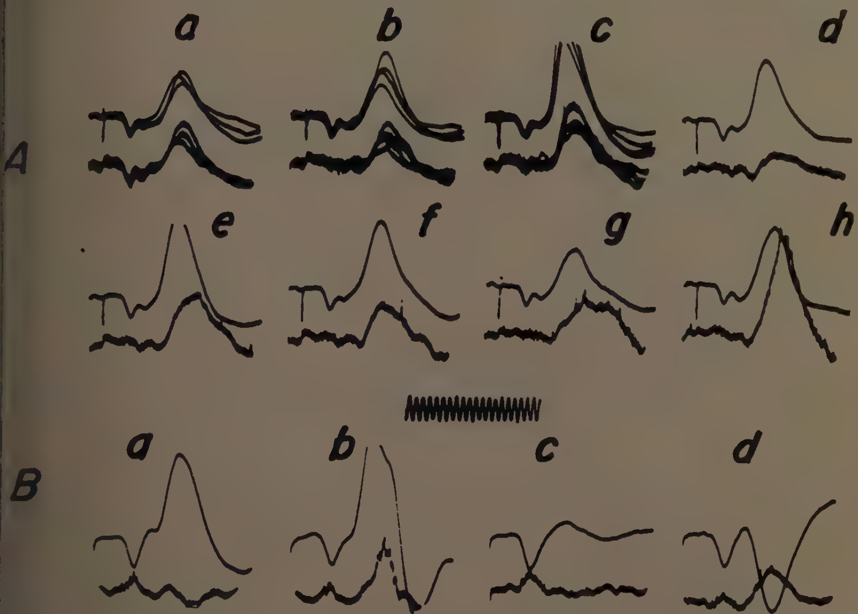


FIGURE 7. The postactivation facilitation of evoked responses in the nonspecific cortex suprasylvian gyrus) in a two-day-old kitten. The stimulation was applied to the medial ortion of the lower mesencephalon.

Aa shows the evoked responses recorded from the cortical surface with a ball-tipped electrode (*upper channel*) and an adjacent saline-filled micropipette (*lower channel*). *b* is the reading 2 min. after the microelectrode was placed in position 0.4 mm. below the cortical surface. The stimulation in *a* and *b* was 0.5/sec. During 5/sec. stimulation (*c*), the responses recorded t the surface and subsurface loci are enhanced. Between *c* and *d* the stimulus frequency was ncreased to 25/sec. for 4 sec. Responses in *d* to *h* were obtained with 0.5/sec. stimulation uring the postactivation period. Dissociation of the effects at surface and subsurface sites clearly seen, especially in *d* and *h*. See text for further explanation.

B shows substantially the same experiment as *A*, but stimulation was applied in more ostral mid-brain regions. *a* shows the microelectorde (*lower channel*) record from a position .55 mm. below the cortical surface. At this site the phase reversal of the initial surface-positivity is complete and late surface-negativity is reflected in a small subsurface focal positivity. shows an early phase of the postactivation facilitation, as in *Ae*. *c* is the result 30 sec. after ntravenous injection of 100 mg./kg. of GABA. The long-latency surface-negativity is abolhed. During the GABA action, long-latency surface-positivity is unmasked in the post ctivation period (*d*), but the polarity of focal responses is similar to that recorded prior to the tion of the ω-amino acid. Calibration: 100 cps; 0.1 mv.

onstitute almost the entire receptor surface area of cortical pyramidal neurons the immediate neonatal period. An axosomatic origin of the prior surface ositivity that, incidentally, is completely unaltered during postactivation otentiation, is suggested by the fact that it is associated with negativity in e cortical depths and is unaffected by GABA.[5] Suffice it to say that in the eonatal period all the characteristics of the long-latency surface negativity own in FIGURES 5 to 7 can be observed in anterior suprasylvian gyrus re-

sponses devoid of prior surface-positive components (see below). Thus th dramatic alterations in evoked responses in the nonspecific projection corte subsequent to brief changes in stimulus frequency, would appear to be attrib utable to functional changes that occur exclusively in axodendritic synapt organizations.

"Integrative Action" of Axodendritic Synaptic Organizations in the Association Cortex of Newborn Cat

The alterations in superficial axodendritic pathways revealed by shor interval paired stimuli to "nonspecific" projection pathways in the thalamu are also seen with stimulation of medial pontomesencephalic regions in nev born animals. High-frequency stimulation of these regions in favorable prep rations of newborn kittens produced striking alterations in surface activit that were detectable over wide areas of the suprasylvian gyrus. In prepar

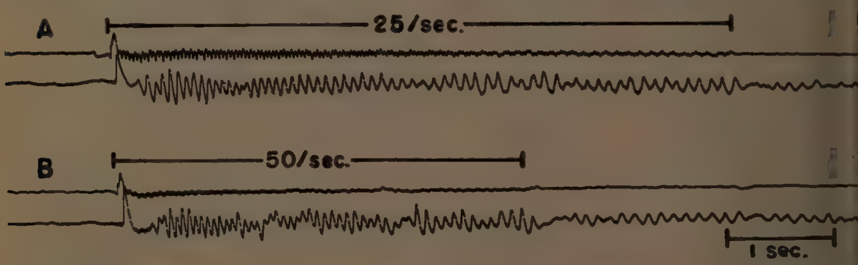


FIGURE 8. Evoked electrocortical activity from the posterior sigmoid gyrus (*upper cha nel*) and the anterior suprasylvian gyrus (*lower channel*) during 25 to 50/sec. brain stem sti ulation in a one-day-old kitten. The evoked activity in the specific cortex is blocked at th stimulus frequency, whereas activity in the nonspecific cortex consists of 12 to 14/sec. surfa negative potentials that persist at 10/sec. for a few seconds after cessation of the stimulati See text for further explanation.

tions exhibiting insignificant spontaneous electrocortical activity, high-fr quency brain stem stimulation at 25 to 50/sec. induced an initial high-amp tude evoked response in both the postsigmoid and anterior suprasylvian gyru but only in the latter was this followed by the development of 12 to 14/se high-amplitude oscillations. Cessation of the electrical stimulus was ass ciated with a brief phase of electrical "silence," followed by the appearance a slower (10/sec.) rhythm (FIGURE 8). Similar events observed in the anteri suprasylvian gyrus in another neonatal preparation are shown in greater d tail in FIGURE 9*A* and *B*. It appears from this figure that although the ma nitude of the initial complex initiated by 25 to 50/sec. brain stem stimulati may be due to the facilitatory action of the first few short-interval stimu (see FIGURE 6), the progressive development of 12 to 14/sec. brain waves duri stimulation, the brief "silence" afterward, and the reappearance of 10/se rhythm suggest that changes other than those related to activity cycles evoked nonspecific responses play a role in the development of driven 10 14/sec. electrocortical potentials. Some evidence for this is provided by t effects that rapid changes in stimulus frequency produce on responses evok by 0.5/sec. stimulation of the pontomesencephalic "reticular" regions.

FIGURE 9C the last of a series of responses evoked every 2 sec. (0.5/sec.) is shown before a frequency change to 10/sec. The latter stimulus frequency elicited a few high-amplitude evoked responses, then 10/sec. "driving." Upon cessation of the 10/sec. stimulation and resumption of the 0.5/sec. stimulus, the tested responses exhibited relatively insignificant changes in magnitude. In contrast, when the stimulus frequency was changed from 0.5/sec. to 25/sec. (FIGURE 9D) or 50/sec. (9E), the tested responses underwent extraordinary increases in amplitude that persisted for many seconds.

The complex sequence of alterations in tested nonspecific responses in the anterior suprasylvian gyrus, subsequent to and following changes in stimulus frequency, are shown in detail in FIGURE 10. In this figure, *Aa* (*lower left*)

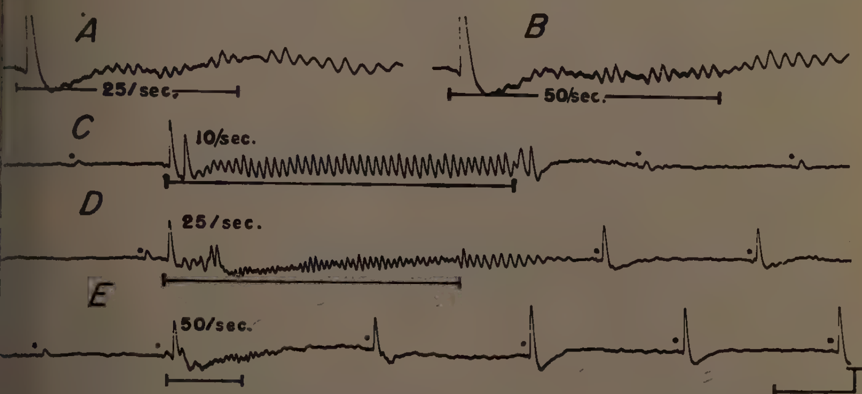


FIGURE 9. Alterations in the surface-evoked responses in the anterior suprasylvian gyrus during and after medial pontomesencephalic stimulation in a two-day-old kitten. Note the prominent evoked potential and the 10 to 14/sec. waves persisting after the 25/sec. (*A*) and the 50/sec. (*B*) stimulation. *C*, a low-amplitude response evoked by 0.5/sec. stimulation, is shown (*black dot*) prior to a change in stimulus frequency to 10/sec. After cessation of the 10/sec. driving stimulus a minimal change occurs in the 0.5/sec. evoked responses. *D* and *E* are the same experiments as *C*, but the stimulus is changed from 0.5/sec. to 25/sec. in *D* and to 50/sec. in *E*, as indicated. Note the profound postactivation facilitation, especially after the short 50/sec. burst. The time calibration in *A* and *B* represents 0.5 sec.; in *C*, *D*, and *E* it is 1 sec.

indicates the *first* response evoked after a 30-min. period of inactivity, *Ab* to *Al* indicate responses evoked every two seconds thereafter. *S* signals a 4-sec. period of 25/sec. stimulation, after which the sequence *Ba* to *Bff* represents 0.5/sec. evoked responses. Particular attention is focused on the magnitude of the first response (*Aa*) after the 30-min. rest period, the gradual reduction and virtual disappearance of subsequent 0.5/sec. evoked responses, the marked and prolonged facilitation of tested responses after 25/sec. stimulation, and the disappearance prior to and the reappearance of tested responses after another period of 25/sec. stimulation. Graphic representation of results similar to those shown in FIGURE 10, but from another series, is presented in FIGURE 11. In the latter figure, peak-to-peak amplitudes of 0.5/sec. surface-evoked responses are plotted with respect to time. Disappearance of responses during 2 min. of 0.5/sec. stimulation was followed by marked facilitation after a 4-sec. period of 25/sec. stimulation. When the amplitude of evoked re-

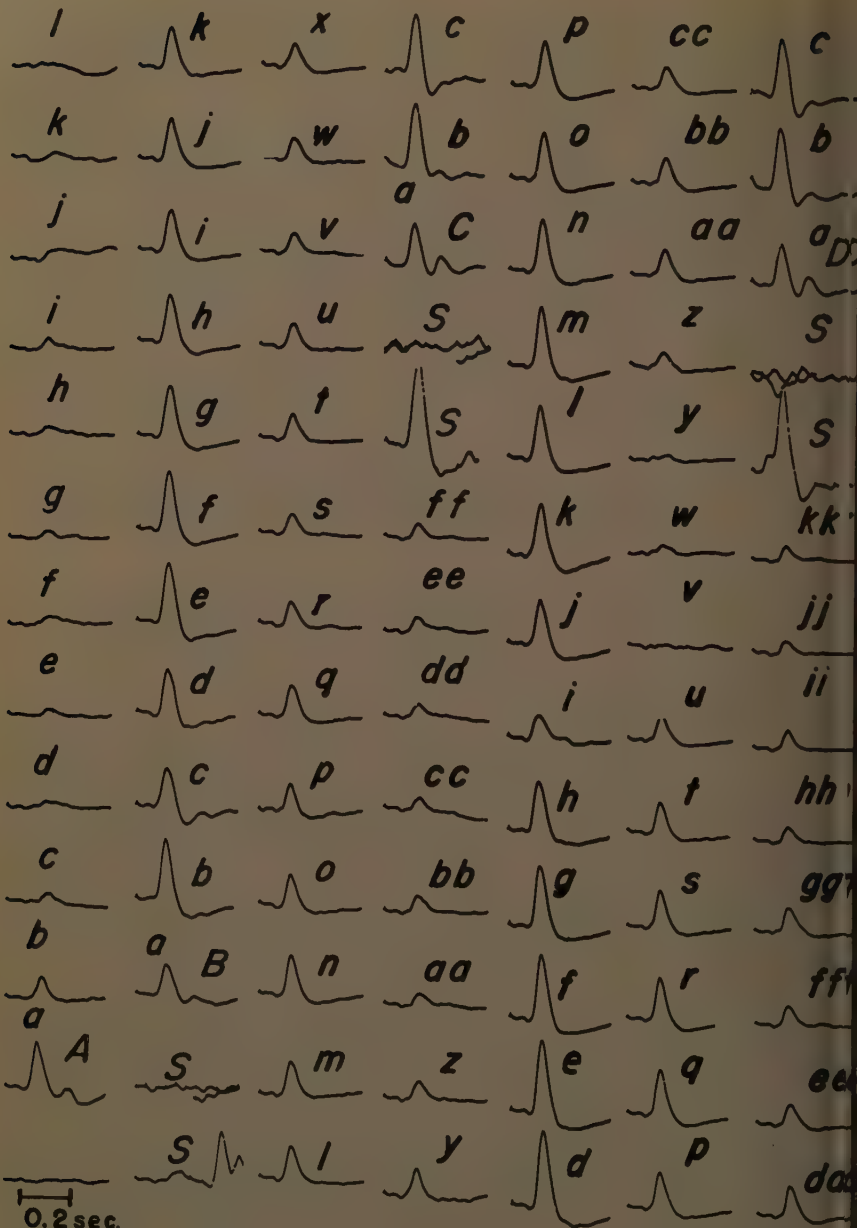


FIGURE 10. A continuous series of surface responses in the anterior suprasylvian gyr evoked by a 0.5/sec. brain stem stimulation for 3 min. The figure is to be read from the low left to the upper right. The first series (beginning at *Aa*) was begun after a 30-min. rest peric Note the rapid disappearance of response during the 0.5/sec. stimulation, and facilitati after 4-sec. bursts of 25/sec. stimulation (S–S). Series *B* shows a one-minute period of pos activation facilitation. The cyclic changes in responsiveness occasionally observed duri postactivation facilitation are shown in series *Ca* to *Ckk*.

ponses decreased again another 25/sec. burst was introduced. This sequence was repeated until the interposed 25/sec. stimulus produced little postactivation facilitation. At this stage, the initial magnitude of the facilitation was partly restored by a 50/sec. burst and, when the facilitatory action of this burst was dissipated, a subsequent 25/sec. burst initiated a phase of postactivation facilitation that was of greater intensity than that associated with the previous 25/sec. stimulus.

In neonatal preparations in which responses were simultaneously recorded from the posterior sigmoid and anterior suprasylvian gyrus during experiments

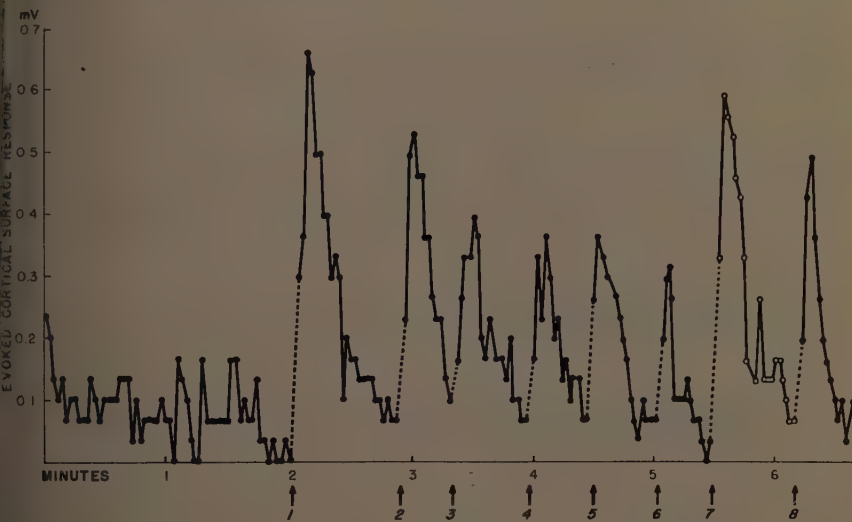


FIGURE 11. A graphical representation of data similar to those shown in FIGURE 10, but from another continuous series lasting more than six minutes. The amplitude of 0.5/sec. evoked responses in the anterior suprasylvian gyrus rapidly decreases over a two-minute period. At the first arrow, the stimulus frequency was abruptly changed to 25/sec. for 4 sec. (dotted portion of curve). The postactivation facilitation of the 0.5/sec. evoked responses is profound initially, but during continued presentation of the 25/sec. stimulation (arrows 2 to 6) it becomes less effective. The magnitude of the postactivation facilitation is partially restored after 50/sec. stimulation (arrow 7, the series with open circles) and again with 25/sec. stimulation (arrow 8).

identical to those illustrated in FIGURES 10 and 11, prolonged postactivation facilitation of long-latency surface-negativity was restricted to organizations in the anterior suprasylvian gyrus (FIGURE 12). Thus the sustained facilitation of evoked responses subsequent to changes in the temporal pattern of brain stem stimulation appears to be entirely attributable to local changes in related axodendritic organizations in the association cortex, and not to secondary changes due to generalized alterations in cerebral hemodynamics.

Although little is known at this time about the composition or the sites of origin of the corticipetal projections whose high-frequency stimulation evokes 10 to 14/sec. synchronous activity in the neonatal cat suprasylvian cortex, available data suggest that such pathways involve intralaminar as well as mid-line thalamic nuclei. Prolonged stimulation of some intralaminar thalamic

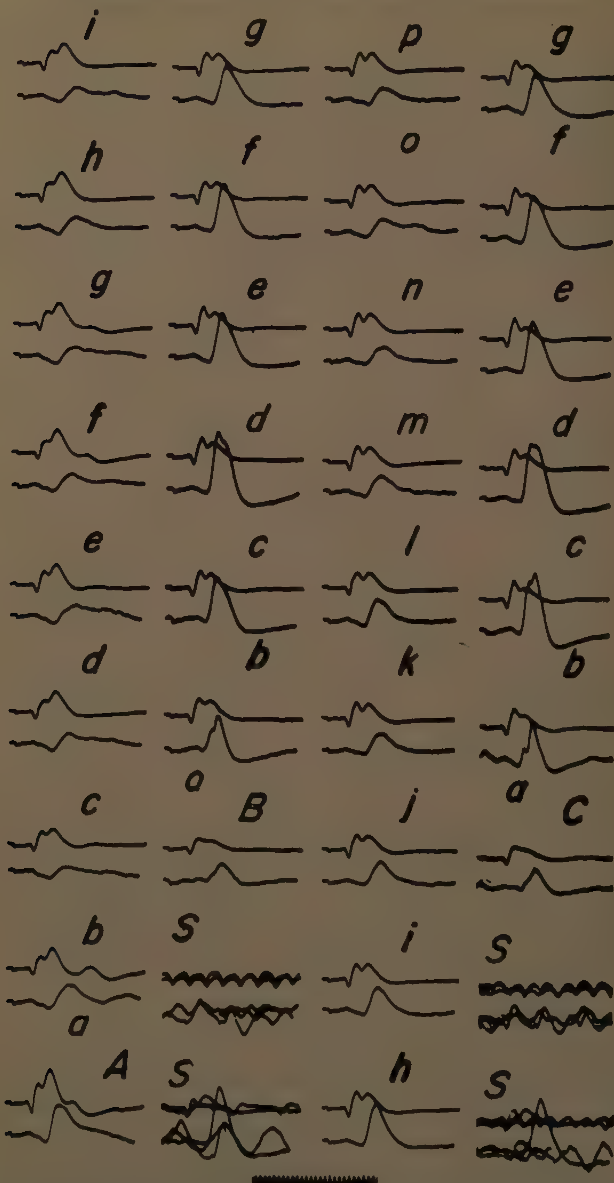


FIGURE 12. Surface-evoked responses in the posterior sigmoid gyrus (*upper channel*) an anterior suprasylvian gyrus (*lower channel*) during 0.5/sec. lower brain stem stimulation in one-day-old kitten. See legend to FIGURE 10 for a detailed explanation of this series. indicates a 4-sec. period of 25/sec. stimulation following series *A* and *B*. Note the selectivi postactivation facilitation of long-latency surface-negativity in the nonspecific projectio cortex. Calibration: 100 cps; 0.3 mv.

regions of newborn cats at 25/sec. often induced a delayed build-up of 10/sec. synchronous activity that was slightly increased in frequency during 50/sec. stimulation (FIGURE 13*A*, *B*). When the stimulus frequency was reduced again to 25/sec., progressive blockade of evoked activity occurred (*D*), but might have been initiated again during the change to a higher frequency (FIGURE 13*D* to *F*). Continuous sequences such as those shown in FIGURE

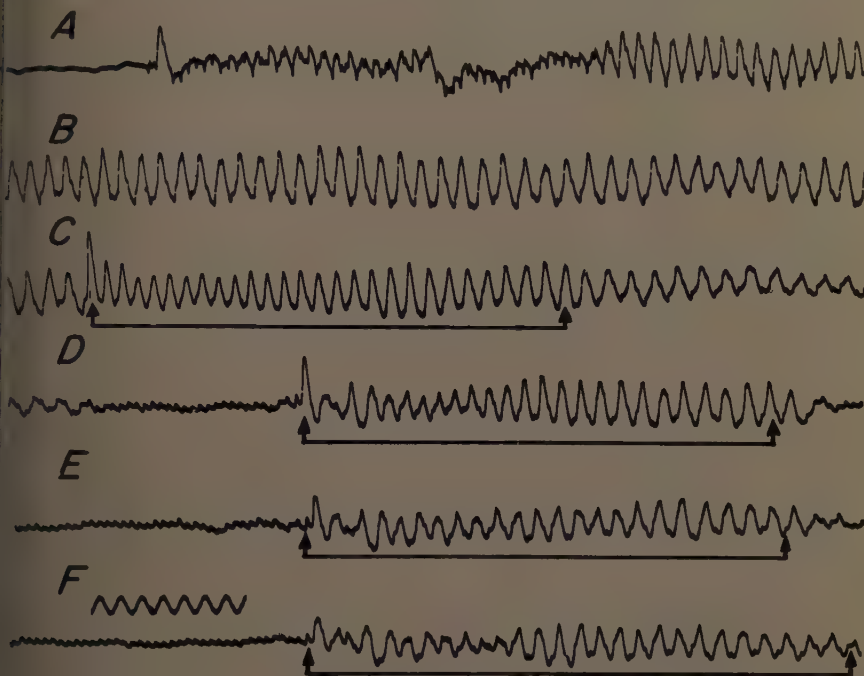


FIGURE 13. Alterations in evoked electrocortical activity in the nonspecific projection cortex (anterior suprasylvian gyrus) following high-frequency intralaminar thalamic stimulation in a two-day-old kitten. Spontaneous electrocortical activity was absent in this preparation at the time of stimulation. *A* to *F* in this figure represent a continuous record. Intralaminar stimulation (25/sec.) was initiated in *A*. The high-amplitude evoked potential is followed by a phase of depressed responsiveness and a progressive build-up of 10/sec. waves driven by 25/sec. stimulation (*B*). In *C* the stimulus frequency is changed to 50/sec. for the period indicated by the arrows, and then reduced again to 25/sec. In *D*, *E*, and *F* frequency changes from 25/sec. to 50/sec. are similarly indicated. Note the blockade of 10/sec. waves during continued 25/sec. stimulation and their reappearance during 50/sec. stimulation. Calibration: 100 cps; 0.1 mv.

13 were recorded in newborn animals prior to the 7th to 10th postnatal day. After this period, more generalized responses of an entirely different character were evoked by stimulation in subcortical regions, yielding the effects described above. Further studies are in progress to define more precisely the operating factors that convert the unique pattern of evoked electrocortical activity observed in neonatal preparations to those recorded in the mature animal.

Comments

The data summarized above illustrate, on the one hand, the analytical value of ontogenetic studies in defining the origin of different cortically evoked syn-

aptic activities and, on the other, the extraordinary complexity of the latte in a developmental stage at which organized spontaneous electrocortical ac tivity is absent and neocortical pyramidal neurons are largely "simple" bipola elements. The data are relevant to the interpretation of evoked cortica potentials and to several aspects of the morphophysiological processes under lying sustained alterations in the functional activity of the brain. With re spect to the nature and origin of superficial negative responses evoked b cortical surface or subcortical stimulation, the close correlation between mor phological and electrophysiological data lends further support to the hypothe sis that these responses represent largely p.s.p.s of apical dendritic elements.[4,1 20,21] However, apart from providing crucial data on the morphophysiologic properties of axodendritic synapses in superficial cortical neuropil of the new born animal, the foregoing results also reveal that in the earliest phases extrauterine life some cortical axodendritic synaptic organizations are capabl of participating in the elaboration of complex electrocortical events. It is interest that in the neonatal period the synaptic organizations involved i these events are selectively developed in the superficial neuropil of some type of nonspecific projection cortex.

Examination of the manner in which these highly differentiated axodendriti synaptic organizations respond to changing patterns of corticipetal volley and to repetition of these volleys without change emphasizes the complexit of these events. Thus p.s.p.s evoked at various loci on apical dendrites b low-frequency (0.5/sec.) "nonspecific" thalamic or brain stem stimulation ar prominent with the first few stimuli; the p.s.p.s then gradually decrease i amplitude until no overt responses are detectable. A sudden change in stimu lus frequency initiates 10 to 14/sec. electrocortical waves; when the stimulu frequency is reduced again to 0.5/sec., prolonged facilitation of evoked re sponses ensues. During the postactivation facilitation period, summate p.s.p.s generated at various apical dendritic loci appear to undergo variatio in magnitude at different times. Continued presentation of a high-frequenc stimulus that originally initiated a period of pronounced postactivation facil tation soon fails to do so; when this occurs, restoration of a prominent pos activation facilitation phase is achieved by changes in stimulus frequency While it is likely that some of these events have much in common with tho underlying posttetanic potentiation and inhibition in other synaptic path ways,[22] it should be emphasized that the important factor in conditioning th excitability of cortical synaptic pathways involved in the production of th tested evoked responses described here is the degree to which different tem poral patterns of corticipetal volleys differ one from the other. Suffice it t say that although little is known concerning the ultimate nature of the mech nisms set into operation by such changes in stimulus pattern, it is clear th many of the attributes of a neuronal aggregate capable of "detecting" varia tions in stimulus patterns are found to be highly differentiated in superfici synaptic pathways in the immediate perinatal period. It would appear fro this fact that alterations in over-all activity that develop in these pathway in response to changes in corticipetal volleys reflect patterns of synaptic a tivities in elements intrinsically organized by processes independent of exog nous influences.

One consequence of the intrinsic organization of elements in the superficial neuropil is seen in the overt effects produced by stimulation of subcortical projection pathways to the "nonspecific" cortex. During 10/sec. stimulation of these pathways in the perinatal cat, evoked surface electrocortical activity is directly related to stimulus frequency. At higher stimulus frequencies (25 to 50/sec.), electrocortical waves are minimally increased to 12 to 14/sec. and persist as a modified "after-discharge" for several seconds. Since the apparent "frequency response" of the axodendritic synaptic organizations involved in the production of evoked electrocortical activity is determined largely by the functional activity cycle of these organizations involved in the production of evoked electrocortical activity, it is not surprising that stimulus frequencies in excess of 10 to 14/sec. do not significantly alter the frequency of the "driven" surface-evoked activity. It is of interest, however, that in the perinatal period relatively high-frequency brain stem or intralaminar thalamic stimulation evokes a pattern of synchronous 10 to 14/sec. surface potentials whose origin in the superficial neuropil is established by a variety of morphophysiological data. Although a discussion of the implications of these findings with respect to the ontogenesis of the EEG is beyond the scope of the present report, it should be noted that in the continued search for the mechanisms involved in the development of organized spontaneous electrocortical activity, attention to the differential rate of morphophysiological development of different synaptic organizations (that is, apical axodendritic, basilar axodendritic, and axosomatic) is likely to provide clues of greater value than have been forthcoming thus far in developmental studies.

The finding that selectively differentiated superficial axodendritic synaptic organizations are capable of exhibiting relatively prolonged alterations in responsiveness, subsequent to either short-term variations in stimulus pattern or continued repetition of the same stimulus pattern, raises the question of the relationship between the electrophysiological events described here in the newborn animal and those observed in association with habituation and dishabituation in complex behavioral situations.[1,23] Allowing for differences in the temporal course of habituation and dishabituation in behavioral experiments (although as is well known "habituation" of some cortically evoked nonspecific responses may be complete after a few presentations of the indifferent stimulus[24]), the remarkable similarity in the electrophysiological events occurring in superficial neocortical neuropil and those found at various levels of the neuraxis during "habituation" and "dishabituation" suggests that those processes operating to increase or decrease the "meaningfulness" of a given signal appear to be built into the chassis of some cortical synaptic organizations well in advance of the complete maturation of the brain.

Of the mechanisms responsible for the electrocortical events in the nonspecific projection cortex that have been viewed here as elementary examples of *electrophysiological* "habituation and dishabituation," little can be said except, perhaps, to caution against seeking oversimplified explanations. For even as one probes deeper into the nature of the fundamental processes underlying the development of enduring changes in neuronal activity and attempts to dissect complex activities into their simplest reflex patterns, one should be reminded of Sherrington's[25] initial notation on the simple reflex: "A simple

reflex is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts, and it is a system certainly never absolutely at rest. But the simple reflex is a convenient, if not a probable fiction."

Summary

Data are presented on the morphophysiological properties of the neocortex in the newborn cat that permit further analysis of the role of superficial axodendritic synaptic pathways in the elaboration of complex electrocortical events. In the immediate neonatal period both specific and nonspecific thalamocortical evoked responses exhibit prominent surface-negative components attributable to synaptic activation of apical dendrites. Superficial axodendritic synaptic organizations in the nonspecific projection cortex differ from those in the specific projection cortex in their responsiveness to relatively high frequency corticipetal volleys. This property is reflected, in part, in differences in overt electrographic characteristics and activity cycles of repetitively evoked specific and nonspecific responses and in the capacity of axodendritic pathways in the nonspecific projection cortex to undergo alterations in excitability during, and for relatively long periods after, brief changes in stimulus pattern. The ontogenetic data are discussed in terms of their relationship to apparently similar electrophysiological events described in other synaptic organizations during "habituation" and "dishabituation" of evoked responses.

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EFFECT OF ANODAL POLARIZATION ON THE FIRING PATTERN OF SINGLE CORTICAL CELLS

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In 1953, at the Nineteenth International Physiological Congress, V. S. Rusi-nov (1953) presented the results of a remarkable series of experiments. Rusino observed that a constant current, low-level (2 to 10 μAmp.) anodal stimulus ap-plied to the motor region for the fore- or hindlimb of the rabbit cerebral corte produced a so-called "dominant focus of excitation." The anodal current di not in itself produce movement, but when a sensory stimulus such as a tone or a light was administered during the current flow a discrete movement correspond ing to the polarized region was noted. The level of polarization was apparentl quite critical since either increase or decrease of current flow prevented a moto response to the interpolated sensory stimulus. Rusinov felt that the connectio so formed between two "analyzers," the motor and auditory, for example demonstrated that extracellular current fields exerting an electrotonic influenc on cell populations played a definite role in the normal connecting functio of brain. Because of some technical misunderstandings, an attempt a fe years later by Morrell and Naquet (1955) to confirm these findings met wit failure. However, in 1958, an opportunity was provided to visit the Sovie Union to attend the Moscow Colloquium on Electroencephalography of Highe Nervous Activity. At that time, Rusinov and his associate, A. Sokolova, hos pitably received my associates and me in their laboratory and spent an entir day demonstrating all the details of this experiment. As a result of tha experience it was possible to confirm the "dominant focus" experiment in ou own laboratory. As a modest repayment for the hospitality of Soviet scientist we take special pleasure in introducing this paper with our own confirmatio of the Rusinov experiment and with some further observations obtained b means of microelectrode recording.

Method

Experiments were performed on 12 adult rabbits and 4 cats. An initia operation was performed with sterile technique under light barbiturate anes thesia. Recording electrodes contained in a polyethylene sheet were insert over the dural surface through bilateral posterior burrholes to the position indicated in the diagram of FIGURE 1. Bilateral anterior bone flaps wer turned to expose the motor cortex of both hemispheres. A bipolar stimulatin electrode was used to define the cortical areas that, when stimulated, produce movement of the contralateral fore- and hindlimbs of the animal. This wa an easy procedure in the cat, but was much more difficult in the rabbit, i which most stimulated points gave rise to movements of mastication. I particular, discrete movements of the hindlimb were rarely observed. Wit

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ufficient diligence, however, points were found that gave predominant move-ıents of one or the other hindlimb, although some bilaterality of response vas always evident. A nylon plug containing two apertures was threaded into he bone flap so that it rested over the motor point for contralateral fore-

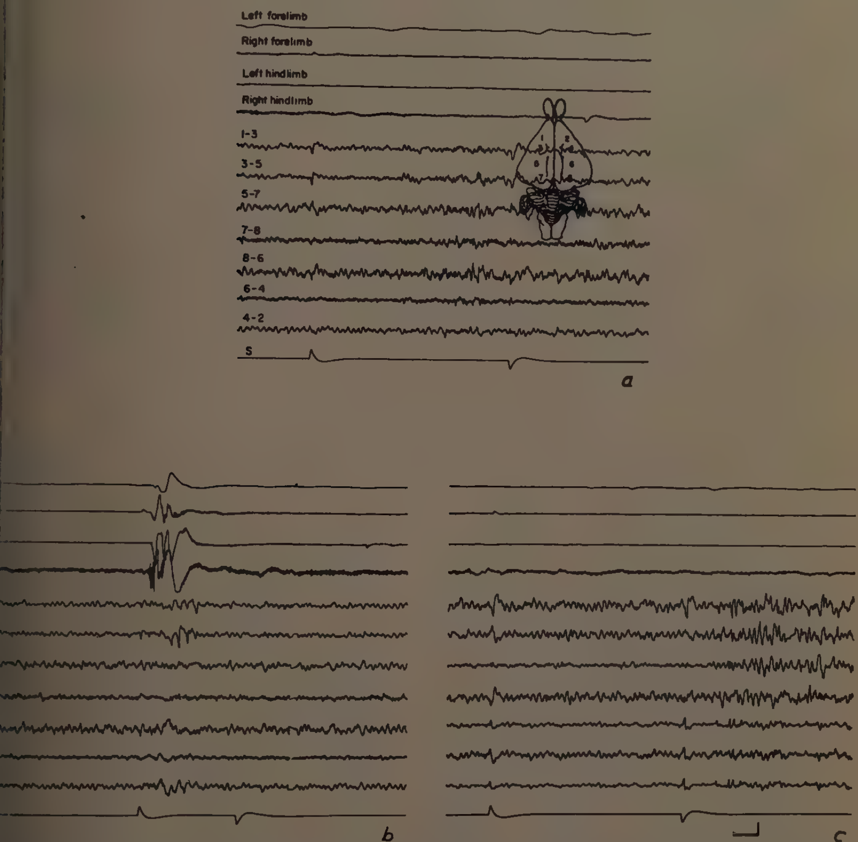

FIGURE 1. Effect of anodal polarization of right hindlimb area on the motor response to ı acoustic signal (tone, 200 cycles per second). The control tracing (*a*) indicates the effect f tone before application of current. During the passage of anodal current (*b*) a complex ıotor response occurred which was maximal in the right hindlimb. One hour after termina-on of polarization (*c*) the tone elicited no motor response. Cortical recording electrodes sted lightly on the dura in the positions indicated in the diagram. The numbering of the ıannels refers to these electrode positions in this and in all other figures of electroencephalo-aphic tracings. *S* indicates the signal channel. Electromyograms are recorded in the up-r four channels. Calibration is 50 μv. and 1 sec. in this and all other electroencephalo-aphic tracings.

mb movement. This was usually in the right hemisphere. In four animals milar plugs were inserted over the corresponding forelimb area in the left emisphere and over the hindlimb area of the left hemisphere. The bone aps were then replaced with wire sutures, and the animals were allowed to cuperate for a period of several months, by which time healing of the bony efect was largely complete.

The experiment itself was performed without anesthesia; the animal was restrained in a device that permitted fairly rigid fixation of the head but free movement of the extremities. Needle electrodes were inserted into each limb for electromyographic recording. Anodal polarization was introduced through a glass capillary electrode filled with saline-soaked cotton and inserted through one of the apertures in the nylon plug. The current source was a constant current stimulator that provided continuous monitoring of the current flow and was usually set to deliver about 10 μAmp. Current return was affected by a connection to the mouth bar of the animal. Peripheral sensory signals were provided by an audio generator and a flickering or continuous light source. In later experiments, a tungsten microelectrode (Hubel, 1957) with a tip diameter of about 5 μ was inserted into the other aperture of the nylon plug for single unit recording. This electrode was connected through a cathode follower and short time-constant amplifier to a conventional oscilloscope. The cortical recording leads were connected to an electroencephalograph. Substitution of the peripheral sensory stimulus by electrical shocks delivered directly to the cortex as well as several operative procedures will be described later.

Results

Behavioral data. Application of the low-level polarizing current produced no motor or other behavioral changes in the animal, nor were there any EEG changes even when the current was maintained for many hours. A tone or light administered in the absence of polarizing current was also ineffective in eliciting motor responses, although EEG changes in the form of desynchronization or evoked potentials were usually seen (FIGURE 1*a*). When an acoustic signal (in this case a 200-cps tone, the onset of which is indicated by the upward deflection on the signal channel and cessation by the downward deflection) was applied against a background of maintained anodal polarization of the cortical region giving rise to right hindlimb movement, a definite movement was seen that was maximal in the appropriate limb (FIGURE 1*b*).

If the polarizing current was discontinued, application of the sound continued to produce a motor response for about 20 to 30 min., after which the effect gradually diminished and disappeared. FIGURE 1*c* illustrates the lack of motor response to the tone one hour after cessation of polarization. Note, however, that the behaviorally inert tone still gave rise to evoked potentials at the "on" and the "off" that were even more pronounced than those seen at the beginning of the experiment (FIGURE 1*a*) or when the sound elicited a behavioral response (FIGURE 1*b*). In our experience the evoked potential was more often augmented when there was no behavioral response than when such response occurred. It was thus negatively correlated with the formation of temporary connections as defined by this technique. In fact, the evoked potentials tended to wax and wane in a more or less random fashion from trial to trial, the amplitude seeming to depend more upon the characteristics of the background rhythm than upon any particular phase of the conditioning procedure.

Occasionally these animals showed signs of spontaneous drowsiness or light sleep, as judged by behavioral criteria such as pupillary miosis and by the

ppearance of slow waves and spindling in the electroencephalogram. During owsy intervals there was a marked increase in the latency of the motor re-ponse to tone. FIGURE 2 demonstrates a control tracing (*a*) in which the one was presented before polarization. The background activity had the oderate voltage rhythmic appearance of the waking animal. There was no otor response. The polarizing current was then turned on and motor re-

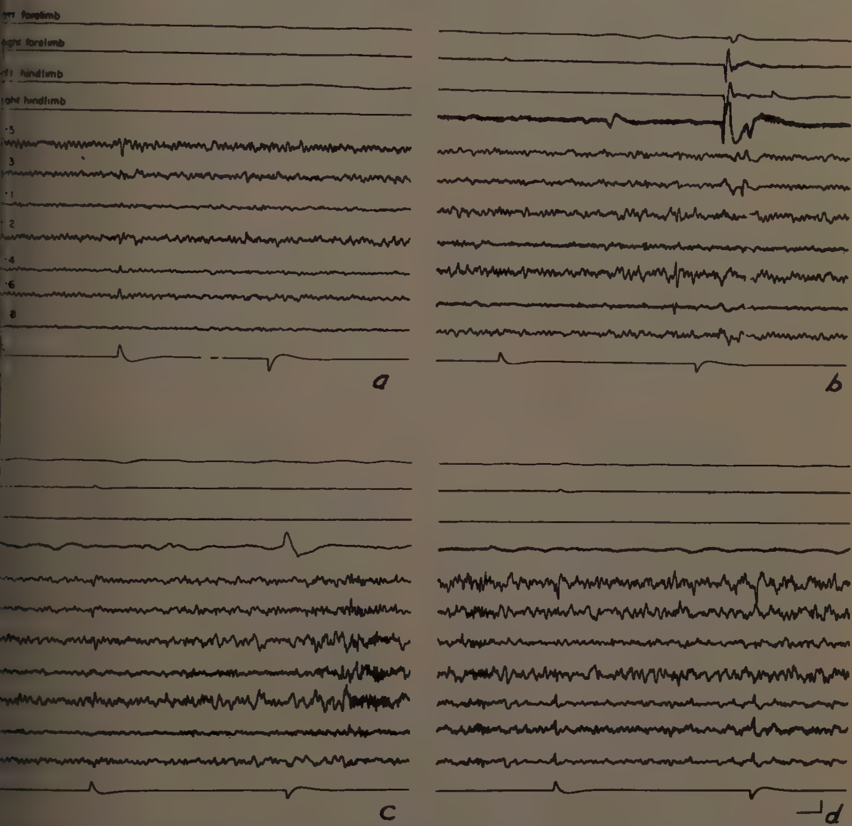

FIGURE 2. Effect of spontaneous light sleep upon the motor response to acoustic stimula-on. The control tracing (*a*) demonstrates the lack of motor response to the acoustic signal esented before beginning polarization. Later in the experiment, the animal became spon-neously drowsy and, although anodal polarization was maintained at a constant level (*b*, *c*, d *d*), the motor-response latency increased (*b* and *c*) and, for one trial (*d*), dropped out com-tely.

onses to the acoustic signal were elicited, as in FIGURE 1*b*. One hour later e animal became spontaneously drowsy (see background EEG in FIGURES , *c*, and *d*), and increased response latency was observed beginning with a all movement at 2½ sec. and a larger more definite one after the cessation tone (FIGURE 2*b*), or a small movement at 5 sec. (FIGURE 2*c*) and no move-ent at all in the next trial (FIGURE 2*d*). Polarization remained constant ring *b*, *c*, and *d*. Again an augmented evoked potential was observed when behavioral response failed (FIGURE 2*d*).

In addition to the phasic motor response to the sensory signal, low-voltag "tonic" muscle potentials were noted throughout the period of polarization i the limb corresponding to the cortical region involved. This was best see when the polarizing electrode was shifted successively from the area for le forelimb to the contralateral homotopic point for right forelimb movemen and, finally, to the cortical region corresponding to right hindlimb movemen (FIGURES 3*a*, *b*, *c*). In FIGURE 3*a*, the muscle potentials appear most prominentl in the left forelimb, with some spillover to the right side. In FIGURE 3*b* th action potentials appear in both right-sided limbs, but more prominently i the forelimb electrodes. Finally, in FIGURE 3*c*, electrodes in the right hindlim show maximum activity with some associated movement of the contralater hindlimb. If one examines each of these records in the sections before appli cation of tone and after its cessation, the tonic muscular activity may be see to shift in location along with the shift of the phasic movement. Forty to 6 min. must be allowed to elapse between the termination of current flow in on area and the beginning of polarization in the next, otherwise overlapping effec will be noted. It seems unlikely that such changes in the routing of the tem porary connection could be explained if the effect of the anodal current we simply to provide another sensory cue by stimulation of trigeminal nerv endings. Indeed, subsequent experiments in which trigeminal neurectom was performed after the manner of Doty *et al.* (1956) have clearly ruled ou such a possibility.

One of our underlying assumptions had been that the effect of anodal curren was simply to sensitize or lower the threshold of a particular region so th any sensory input to the central nervous system would trigger those particul cell populations. Indeed during polarization any transitory event such as handclap, extraneous noise, a puff of air to the animal's face, entrance of th experimenter into the recording cage, or a tone or light stimulus, would trigg the appropriate behavioral response. An attempt to demonstrate differenti conditioning by frequently presenting a tone and rarely or intermittent presenting a light stimulus during polarization was without success. In FIGUR 4 the light (differential stimulus) and the tone (conditional stimulus) a shown to produce no motor effect before polarization (FIGURE 4*a*). Durin polarization (FIGURES 4*b* and *c*) the tone (FIGURE 4*b*)and the light (FIGURE 4 were equally effective in eliciting a motor response, despite the fact that t tone had been presented 30 times and the light only twice in the course of three-hour experiment.

It may be recalled that we had previously noted, as had Rusinov (195 before us, that the effect of anodal current outlasted the period of actu polarization by about 20 min. This is an extraordinary length of time f neurophysiological events, and I am completely unable to explain it in bi physical terms. Nevertheless the investigation of some of the properties this interval has proved particularly fruitful.

The experiment of FIGURE 4 was discontinued and the animal allowed rest for about five hours. At the end of that time, anodal polarization w reinstituted, and the tone previously used as a conditional signal was foun to elicit the same motor response. The light (differential stimulus) was n presented at all. Polarization was then discontinued and, during the ne

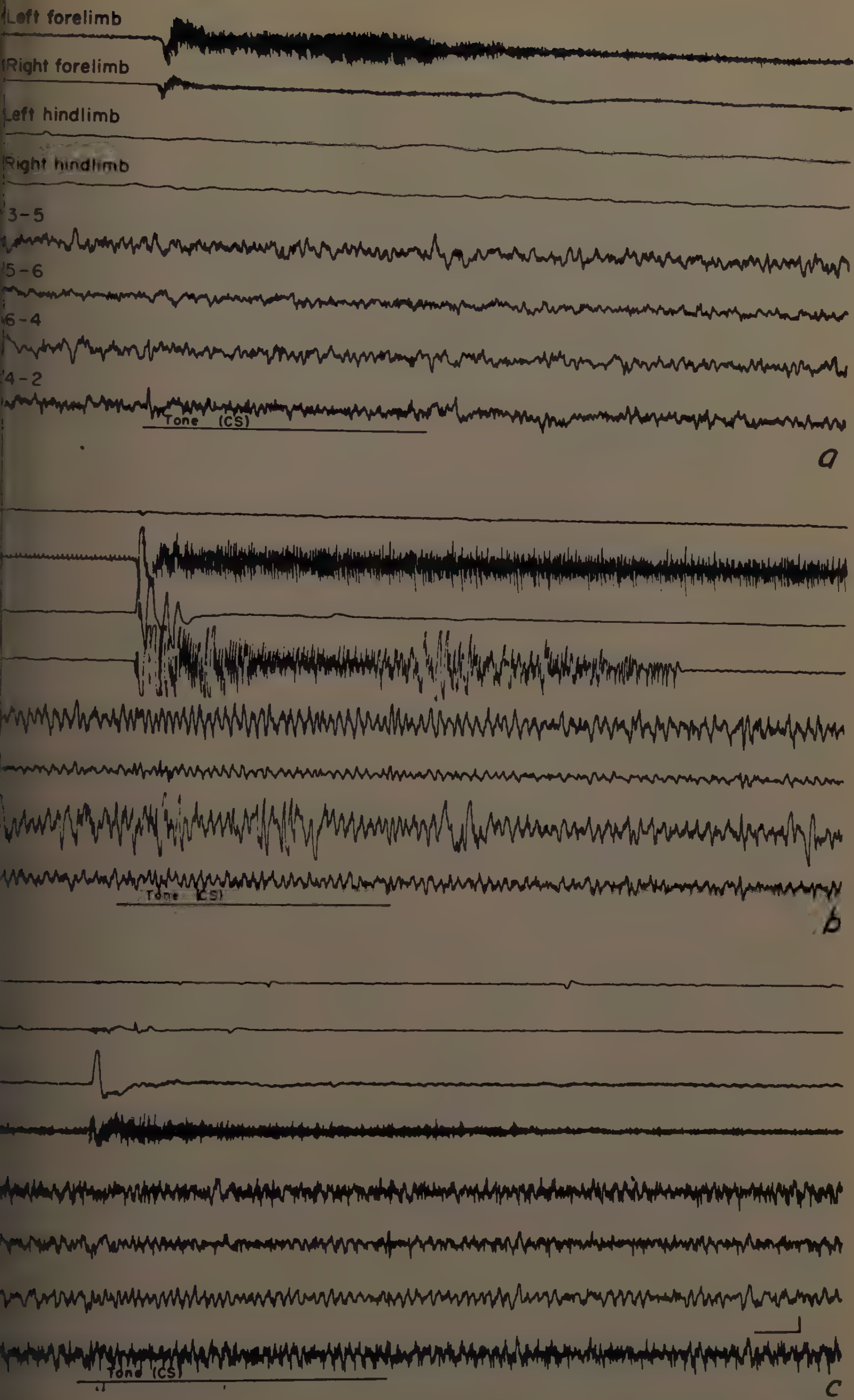

FIGURE 3. Effect of shift in the locus of anodal polarization on the distribution of motor [re]sponse to sound. The polarizing electrode was shifted from the area for left forelimb (*a*) [to] right forelimb (*b*) and to right hind limb (*c*). At least 40 min. were allowed to elapse be[tw]een the termination of current flow in one area and the beginning of polarization in the [ne]xt.

20 min., there were five presentations of tone and five of the light. In eac of the five trials with tone, and in none of the five trials with light was a moto response observed (FIGURE 5). When this result was found to be reproducib in all of the animals, it was assumed, for the first time, that the experime might have some validity as a model of neural learning. Since an environment signal that had been presented to the animal during polarization was found t

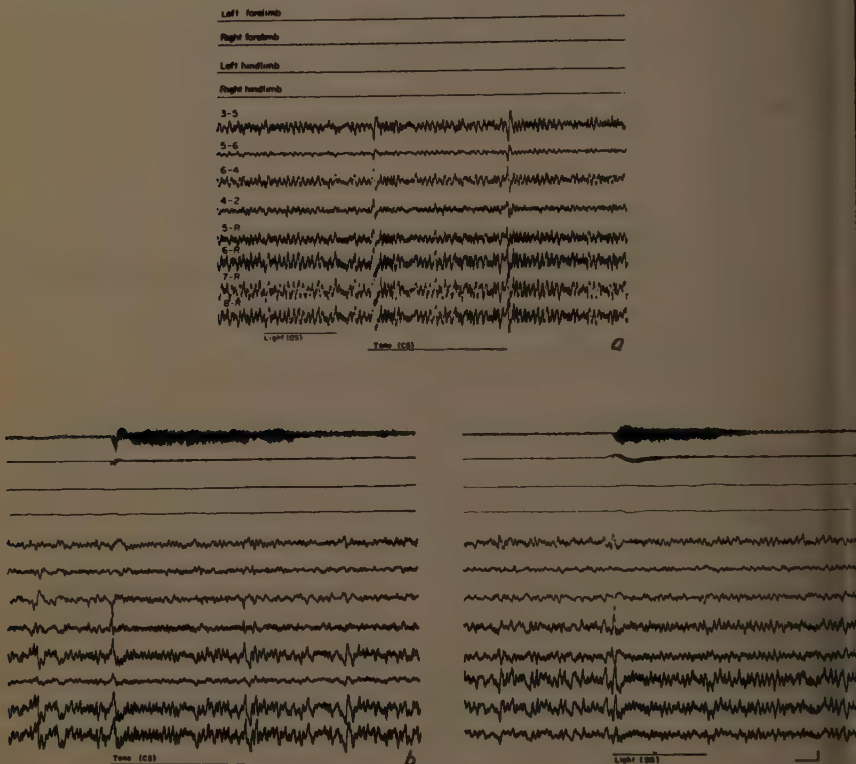

FIGURE 4. "Generalization" of the conditioned motor response. The control traci (*a*) indicated the lack of motor response to light (DS) and to tone (CS) before beginning pol ization. Note that electrocortical responses did occur in the form of evoked potentials at t "on" and the "off" of tone, and smaller evoked potentials plus desynchronization at the "o and "off" of light. During polarization, the tone (*b*) and the light (*c*) were equally effecti in eliciting a motor response.

continue to elicit a characteristic behavioral response in the 20 min. followi cessation of polarization, while another signal that had not been paired wi the anodal current was ineffective in this regard, one must conclude that d ferential conditioning had been established. The cell systems acted upon the polarizing current exhibited at least some of the attributes of short-te memory.

Results of single-unit analysis. Since there was a disappointing paucity electroencephalographic change during the procedures previously outlin microelectrode studies were undertaken in order to provide some informati

bout the behavior of single elements in the polarized region. A microelectrode as inserted through the second aperture of the nylon plug by means of a librated hydraulic microdrive. Prior to polarization, a randomly firing unit as unaltered by administration of a tone of 200 cps (FIGURE 6*a*). The onset nd cessation of tone are indicated respectively by the two upward deflections the second channel of the oscilloscope. During the passage of anodal current, dividual cells were affected by the same tonal stimulus (FIGURES 6*b*, *c*, and). Three distinct response patterns were found. Some cells showed a single urst of high-frequency discharge following the onset of the acoustic signal IGURE 6*b*), others showed an abrupt cessation of discharge (FIGURE 6*c*), and a ird group exhibited bursts of high-frequency spikes at the "on" and at the ff" of the stimulus (FIGURE 6*d*). Of the 210 cells sampled, 82 were of the rst type, 70 of the second, 31 of the third, and 27 cells were unresponsive.

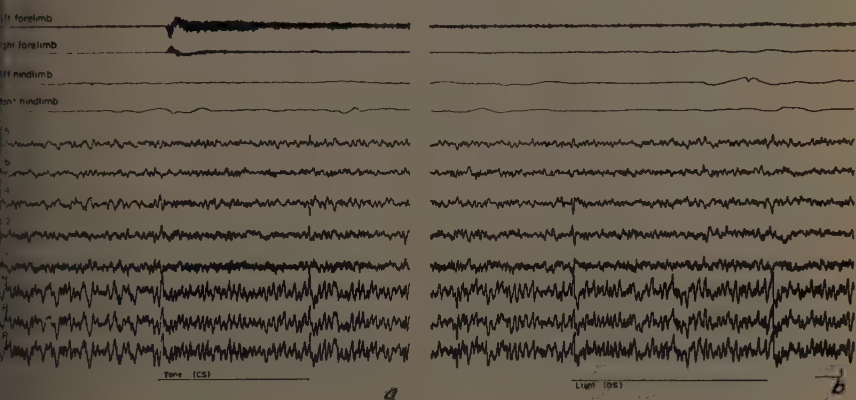

FIGURE 5. Differential motor conditioned response. Twenty min. after cessation of odal polarization the tone (*a*), which had been presented to the animal during polarization, cited a motor response. A light stimulus (*b*) that had never been presented during polarizaon was ineffective.

hus the great majority of cells within the polarized region were active, and the mmonest change observed was an increase in discharge frequency. Most of ese cells were continuously recorded for 30 to 90 min., during which time the sponse pattern to the same stimulus remained true to type. For the sake of evity and simplicity, the remaining discussion will deal only with cells that owed a response pattern of the first type.

Using the experimental procedure illustrated in FIGURES 4 and 5, a differential sponse of single units could also be demonstrated. During polarization a sitive tone (FIGURE 7*a*) and a negative tone (FIGURE 7*b*) were equally effective eliciting high-frequency bursts. Twenty min. after discontinuing polarizaon the positive tone (FIGURE 7*c*) continued to elicit unit discharge, while the gative tone (FIGURE 7*d*) failed to do so. Forty min. after cessation of the odal current, neither the positive tone (FIGURE 7*e*) nor the negative signal IGURE 7*f*) produced any change in unit-discharge frequency.

Doty and Rutledge (1959) have demonstrated that an electrical stimulation the cortex could serve as the conditional stimulus for establishment of a

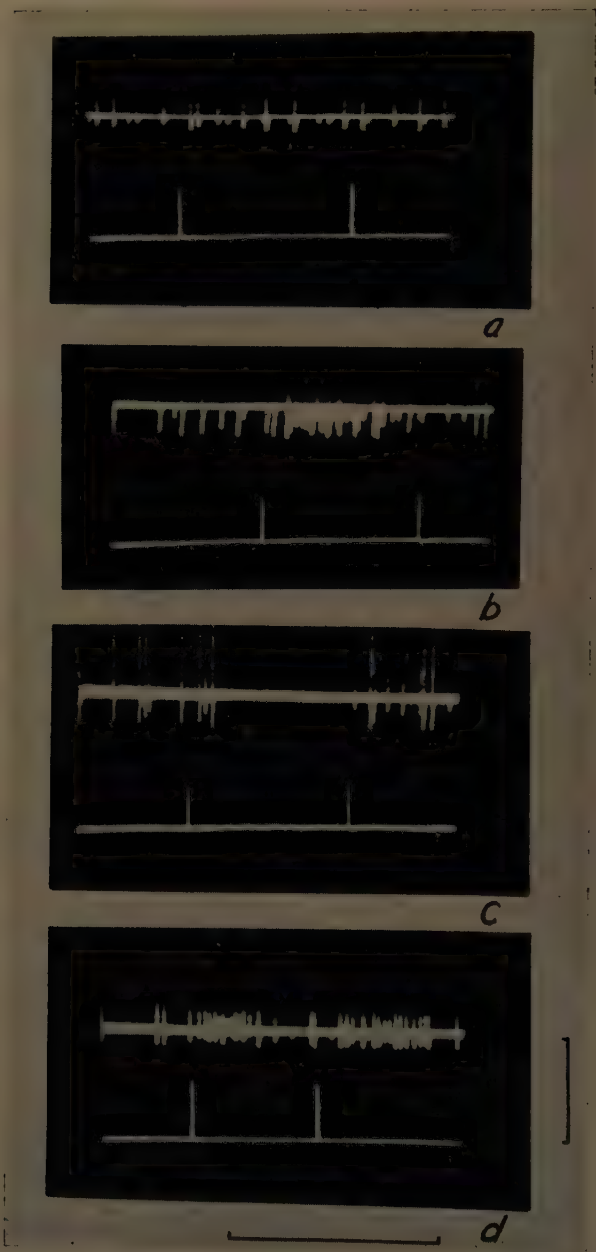

FIGURE 6. Patterns of response in single units to an acoustic stimulus. Duration of t tone of 200 cps is indicated by the two upward deflections in the second channel of the osc loscope. Before polarization (*a*) there was no effect on the discharge frequency of a unit motor cortex. During polarization responses to sound appeared, either in the form of a sing high frequency burst (*b*), a sudden cessation of firing (*c*), or high-frequency bursts at the "o and at the "off" of the tone (*d*). Calibration: 5 mv and 1 sec.

otor-conditioned response. They found definite evidence of transfer when an ectrical stimulus was used to elicit a conditioned response previously elabo-ted to a peripheral signal, as well as when a peripheral signal was used to elicit response previously elaborated to direct cortical stimulation. Doty and urgea (1959) also demonstrated that conditioned responses could be obtained

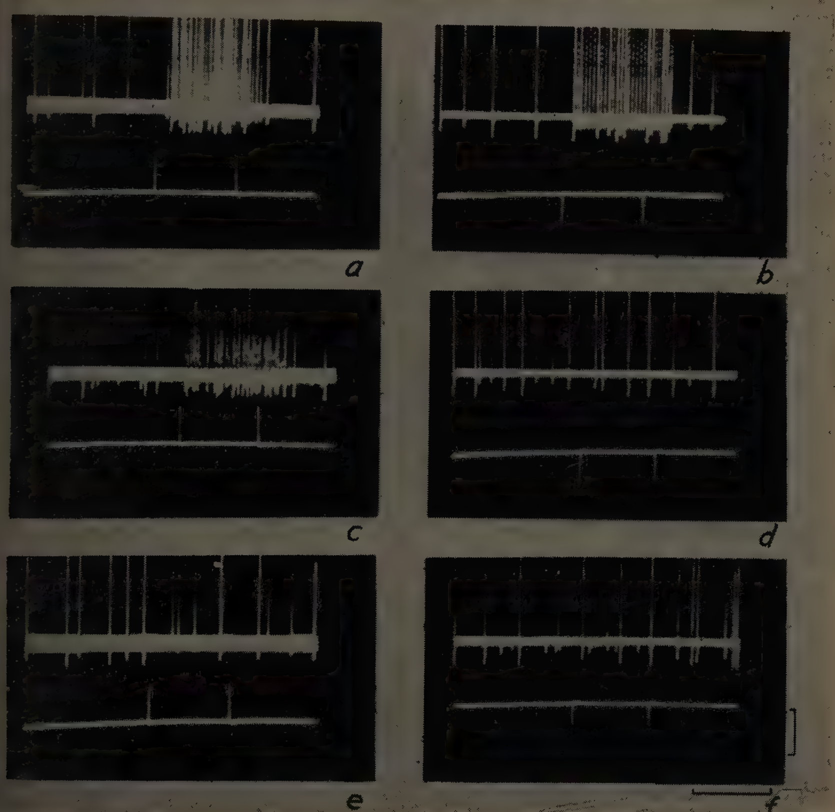

Figure 7. "Generalization and differentiation" in single-unit responses. During the ssage of anodal current (*a* and *b*) the positive tone (*a*) and a single presentation of the nega-e tone (*b*) were equally effective in provoking high-frequency bursts. Twenty min. after sation of current flow (*c* and *d*) the positive tone (*c*) continued to elicit the response, while negative tone (*d*) did not. Forty min. after discontinuing polarization (*e* and *f*) neither nal produced any change in unit-discharge frequency. Calibration: 2 mv and 500 msec.

en the conditional signal was an electrical shock to one hemisphere and the conditional signal an electrical shock to another hemisphere. Their observa-ns provide a useful tool for analysis of the essential anatomical substrates of conditioned response, since the pathways involved may be more precisely termined and much abbreviated.

The animals of this series were subjected to an acute experiment involving de exposure of the cortical surface of both hemispheres under ether anesthe-

sia. The ether was allowed to dissipate and the animals were immobilized wi Flaxedil and artificially ventilated. The polarizing electrode was applied to t motor cortex as before, and the microelectrode inserted directly beneath Since a behavioral response was impossible, we were concerned here only wi the manifestation of a temporary connection as expressed by the conditioning a single-unit discharge. One bipolar stimulating electrode was placed on t cortical surface ipsilateral to the microelectrode placement, at a distance of to 2 cm. A second stimulating electrode was placed on the opposite hem sphere. The stimulating electrodes delivered a 100-msec. burst of 100-pe second pulses, 4 to 8 v in magnitude. The onset of the ipsilateral burst indicated by an upward deflection of the signal channel, and its cessation by downward deflection. Reverse directions signify the contralateral stimulati electrode (FIGURES 8 and 9). Prior to polarization (FIGURE 8*a*), the ipsilater shock did not provoke a change in unit-discharge frequency. The anodal cu rent was then applied (FIGURES 8*b* and *c*), and the ipsilateral shock effective elicited an increase in unit-discharge frequency (FIGURE 8*b*). This was pr sented repeatedly over a 30-min. period. A single test shock at the contrala eral cortical electrode was also effective during the time of polarization (FIGU 8*c*). Twenty min. after discontinuing the anodal current (FIGURES 8*d* and the ipsilateral shock was effective (*d*), while the contralateral (*e*) was no Forty min. later (FIGURES 8*f* and *g*), neither stimulus provoked a change in un responses.

If one examines FIGURE 8*d* carefully, it is apparent that there are two com ponents to the unit response pattern. The components were separated mo clearly when the distance between the stimulating electrode and the recordi microelectrode was increased. The initial event seemed to have a short fix latency independent of the position of the stimulating electrode. The secon component had a longer and more variable latency and, when the distance b tween the stimulating and recording electrodes was short, the two componen merged and were indistinguishable. The two components were not just "o and "off" responses to the stimulus. Each was conducted through a separa anatomical pathway. The two components of the response seen in FIGURE could be dissected apart by a subpial circumsection of the area containing t polarizing and microelectrodes that severed all transcortical connections b left the subcortical connections intact. The result of that procedure is shown FIGURE 9*b*, where only the short latency initial response is evident. Unde cutting of the same region that sectioned the subcortical projections but le the transcortical pathways intact (FIGURE 9*c*), abolished the short laten response but still allowed the late response to appear. A precise measureme of these latencies was difficult since we were dealing with a change in rate (t delta *f* of Fessard, 1960) rather than with a potential having a clearly defin onset. Judging the latency with the unaided eye at best could be only approximation. The use of data processing computers, which were not ava able to us, would have made this task much easier. Yet even with these rese vations, a fairly good linear relationship could be established (FIGURE 10) b tween the distance separating the stimulating and recording electrodes and t latency of the late response. It should be noted that the absolute values va

onsiderably from animal to animal and with change in the general state of any iven animal. The measurements recorded in FIGURE 10 were all made within he space of a few minutes from a cat in which the state of the cortex appeared o be fairly good, as judged by electroencephalographic tracing.

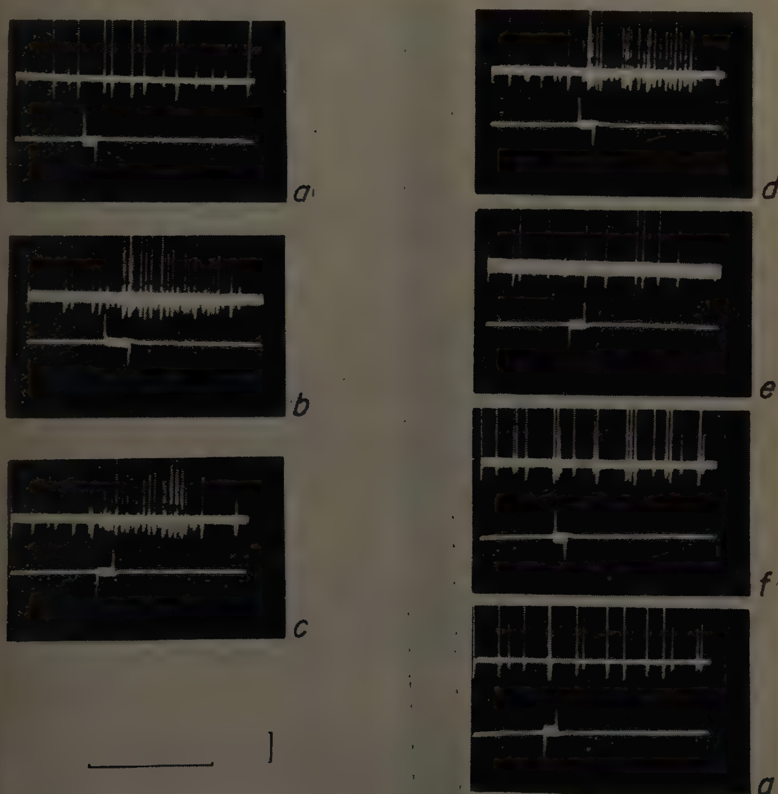

FIGURE 8. Substitution of cortical electrical stimulus for the peripheral sensory signal. he ipsilateral (positive) cortical stimulus is signified by an upward, followed by a downward, flection on the second channel of the oscilloscope. The contralateral (negative) cortical imulus is signified by reverse deflections. Both stimuli are 100-msec. trains of 100-per-cond pulses, 4 to 8 v in magnitude. Before polarization (*a*) the positive stimulus elicited change in unit discharge. During polarization (*b* and *c*) both positive and negative sig-ls were effective. Twenty min. after cessation of current flow (*d* and *e*) the positive signal as effective (*d*), whereas the negative signal was not (*e*). Forty min. after termination of rrent flow (*f* and *g*) neither signal was effective. Calibration: 2 mv and 1 sec.

Discussion

If one takes an anthropomorphic view of the nerve cell in this situation, it is ear that the temporal relationship of these two components of the response to single stimulus could serve to provide the cell with information concerning

FIGURE 9. Separation of the two phases of the unit response to cortical stimulation. the intact brain the biphasic response to cortical shock is shown in *a*. A subpial circumsect of the area containing the polarizing and microelectrodes that severed all transcortical c nections, but left subcortical connections intact (*b*), eliminated the long-latency response l preserved the short-latency one. Undercutting (*c*) without circumsection eliminated short-latency, but preserved the long-latency response. Calibration: 2 mv and 1 sec.

source of the stimulus. The early response had a latency of the order of a r milliseconds and was propagated via a subcortical pathway. The con- ncy of the latency, regardless of the cortical area stimulated, suggests per- ps that a common neuronal pool was activated. Future research employing ective subcortical coagulation and/or recording may, of course, permit ctionation of the early response still further, that is, there may be more than e subcortical component. In any event, the demonstration of at least two

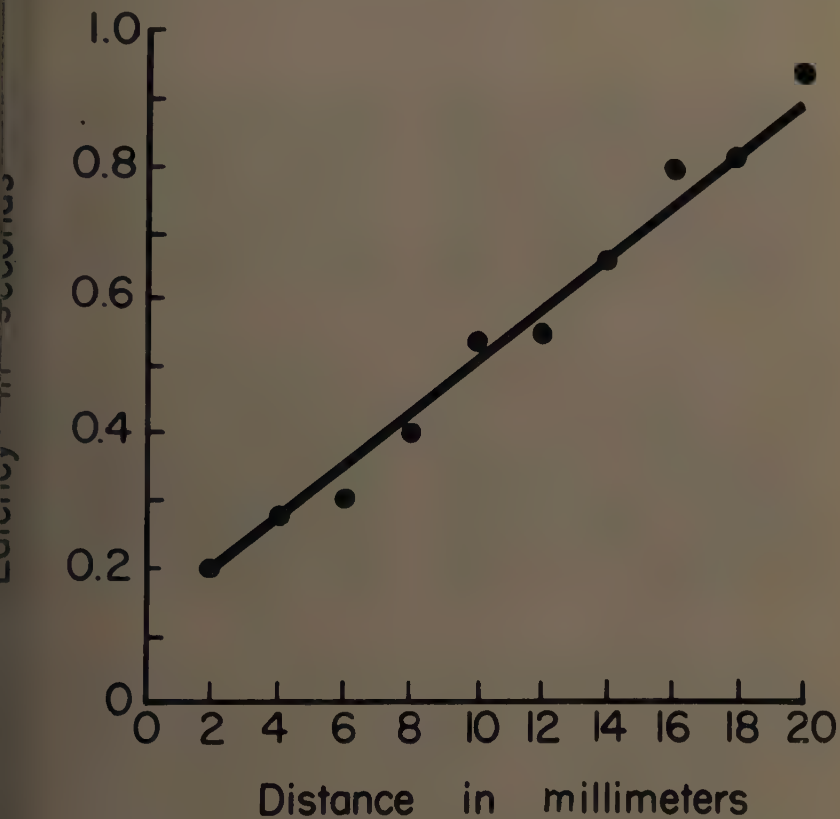

Figure 10. Latency of the late response in undercut cerebral cortex as a function of the tance between stimulating recording and electrodes.

naptic pathways impinging upon a single cellular element might enable the l to compare a new pattern of afferent input with previously established tterns of synaptic engagement. Arrangements such as this might provide a sis for the phase-comparator mechanisms suggested by Adey *et al.* (1960), or the frequency comparison suggested by Brazier (1960) and by John and Kil- n (1960). Certainly the complexity of organization observed in this simplest temporary connections renders any hypothesis based upon simple linear links m sensory to motor centers untenable. Furthermore, it is quite evident that recording of the all-or-none discharge of single cells provides only a frag-

mentary glimpse into the integrative processes that may be going on in graded response tissue of the dendritic tree.

The role of the anodal current in making these observations possible is s obscure. The mechanism would appear to be electrical, however, rather th one of chemical injury, since the effect is abolished by momentary reversa current flow. The constant current may mimic the steady potential field normal cortex. While such fields may not be discrete enough to carry co information (Eccles, 1958), they may provide the means for establishing intercellular synchrony considered by Livanov (1960) to be an essential st

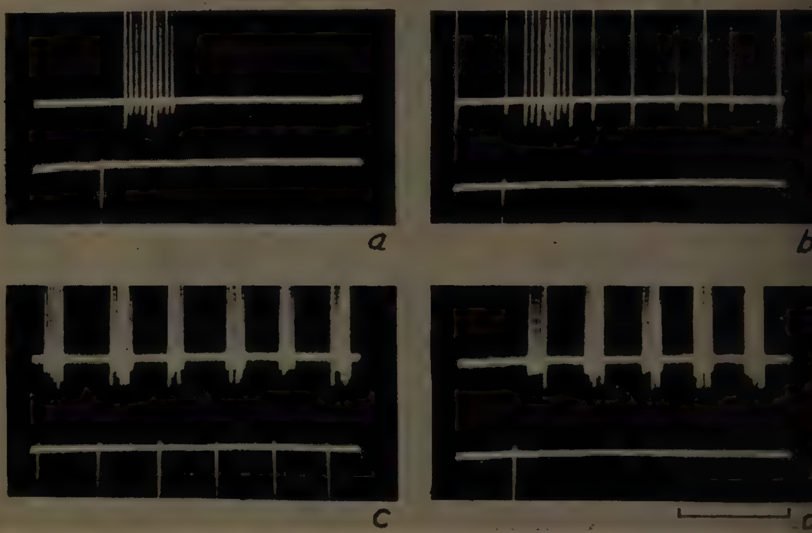

FIGURE 11. Conditioning of a rhythmic burst response to a single flash. Anodal p ization was applied to the visual receiving area. Single flash elicited a single burst in a escent (*a*) and in a randomly firing cell (*b*). Three-per-second stroboscopic stimulatio produced driving of unit discharge at that frequency. A single flash (*d*) delivered 30 after termination of the rhythmic stimulus resulted in repetitive unit discharge at about 3 Unit potentials are seen in the upper channel of the oscilloscope, stimulus artefacts in lower channel. Amplitude calibration: 2 mv. Time calibration: 500 msec. (*a* and *b*) a sec. (*c* and *d*).

in the developing conditioned reaction. In addition to lowering the thresh of the involved cells (Burns, 1954, 1955), the anodal current appears to co upon these cell populations the property of retaining, at least for a short pe of time, a representation of a stimulus imposed during the polarization. Ind this may be demonstrated even more graphically if one shifts the polari electrode to the visual cortex and studies the effect of single or rhythmic str scopic stimulation. FIGURE 11*a* illustrates the burst response to a single f of a relatively quiescent cell in the visual cortex. A randomly firing cell (URE 11*b*) also exhibited a single burst to a single flash. The maintained an polarization made it extraordinarily easy to drive a single unit in burst respo at a 3/sec. flash frequency (FIGURE 11*c*). If such driving was continued f

minutes and then stopped, a single flash delivered 30 sec. later almost al-ys elicited burst responses at the frequency of the original rhythmic flicker. gle flashes delivered at intervals longer than 30 sec. were less and less likely provoke such rhythmic response, but occasional rhythmic responses to single h were noted as long as 20 min. after the rhythmic stimulation was discon-ued. This seems a particularly clear illustration of the capacity of polarized ls to retain some representation of an imposed stimulus pattern for a rela-ely long period of time. The order of magnitude of this time interval is itself nificant. It correlates well with the data of Duncan (1948) on the abolition a learned response in rats consequent to massive electroshock delivered at ious intervals following the training session. It also correlates with clinical perience on the duration of amnesia produced by electroconvulsive therapy l with the amnesia secondary to cerebral concussion. Brazier (1960) has viously pointed out that the enduring neural changes that are the basis of g-term memory of the sort not abolished by sleep, by concussion, or by elec-shock probably will not be found by electrophysiological measurements. wever the synaptic changes that underlie short-term memory and are sensi-e to the effects of anesthesia, sleep, and concussion may very well be dis-ned by the probing instruments of the electrophysiologist when he discovers v and where to look for them. I have presented here the very small and tative beginnings of such a search. The "dominant focus" of Rusinov has vided an intriguing tool for this investigation.

Acknowledgment

Sincere appreciation is expressed for the help of Paul Naitoh in the early ases of this work.

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HE INTERPRETATION OF ELECTROCORTICAL POTENTIALS*

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The modern techniques of electrophysiology are relatively easy to apply to e study of the central nervous system. They have great appeal, since they e capable of providing many simultaneously visualized channels of data from e surface of the brain and within the neuraxial masses. As papers presented ewhere in these pages demonstrate, contributions from recordings of the EEG of electrocortical potentials play an important role in this monograph. It ems to me a prime necessity therefore to raise a fundamental question that to any readers of this publication may probably seem unorthodox and, perhaps, en heretical. Nevertheless it is one that is well grounded in theoretical and perimental aspects. The question is: How significant and decisive are elec-ophysiological recordings from the brain?†

The number of neurons in the "head ganglia" is generally estimated at about ^{10}. Allowing what is probably a conservative estimate of 10^3 synapses on the erage for each neuron, there may be 10^{13} or more synapses in the brain, each pable of generating postsynaptic potentials (p.s.p.s). Some of these are citatory, others inhibitory. There are also on the order of 10^{10} axons, all obably capable of generating and carrying spikes and branching to feed the napses. Of course, the whole of this mass is not active at any one time, but a asonable estimate of the instantaneous activity in the brain is still likely to compass an impressively large number of p.s.p.s and of spikes.

How complex this activity is may be gathered from the example of one obably relatively simple system, that of caudate-cortical connections. Stim-ation of the head of the caudate nucleus with brief single shocks gives rise to ther unimpressive potentials that are restricted to a limited area of the cere-al cortex (Mettler *et al.*, 1952). Nevertheless an electrophysiological analysis urpura *et al.*, 1958) discloses that this single stimulus sets into motion activ- in a large number of excitatory and inhibitory pathways (FIGURE 1). Each probably complex, although none has as yet been analyzed in further detail. her kinds of data (cf. Purpura and Girado, 1959; Purpura *et al.*, 1959*a*) also monstrate that the electrocortical potentials manifested in various types of tivity represent very little, indeed, of the true degree of involvement of urons.

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† The question and discussion that follow are concerned with the theoretical aspects of the blem and with the general physiological consequences. The empirical practice of electro-ephalography has brought forth a number of clinical correlations, much as has the similarly pirical use of electrocardiography. Needless to say, empirical findings have their inde-ident validity, although explanations of these findings may be invalidated by inappropriate ncorrect theory.

Electrophysiological and pharmacological data indicate with a remarkab high order of internal consistency for a large variety of experimental conditio that the major contribution to most electrocortical activities is provided l p.s.p.s, both excitatory and inhibitory (Grundfest, 1958*a*; Purpura, 1959; Pu pura *et al.*, 1959*a*, 1959*b*, 1960; Purpura and Grundfest, 1956, 1957). Tl conclusion agrees with, and accounts for, the effects of a number of differe types of drugs, as shown in tests on different neuraxial structures and on d

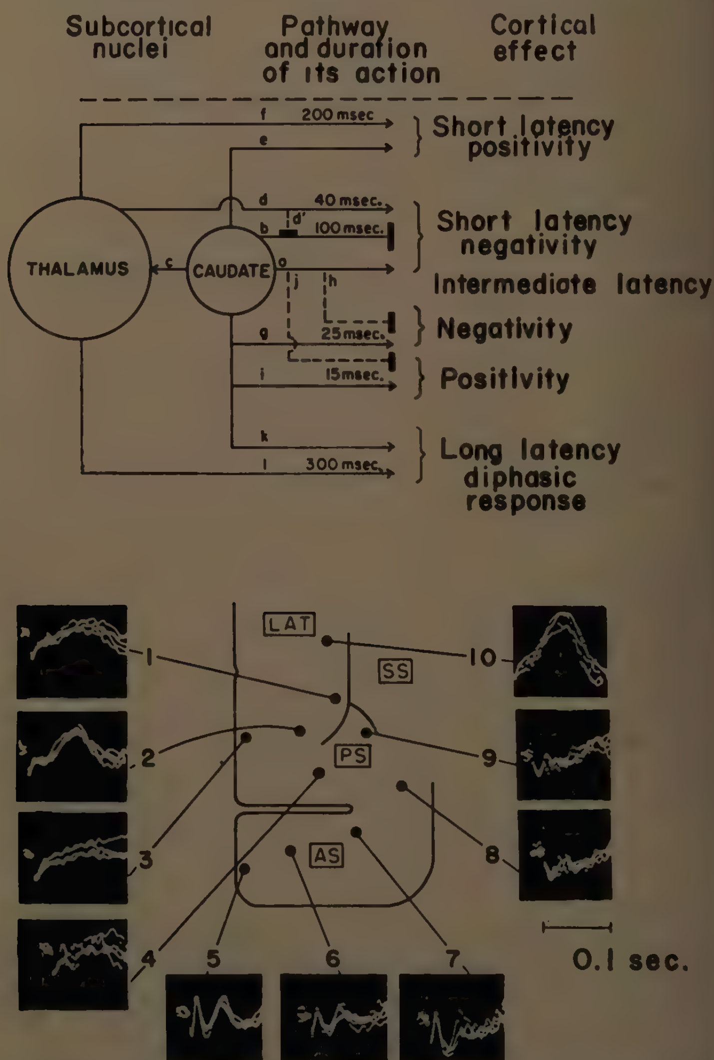

FIGURE 1. Cortical potentials and their underlying actions initiated by a single l stimulus to the head of the caudate nucleus in the cat. Above: a diagrammatic represe tion of the activated corticipetal pathways and their effects. Below: the potentials reco from designated cortical sites in two thirds of the experiments. Reproduced by permis from *Archives italiennes de biologie* (Purpura *et al.*, 1958).

ently evoked activities in a given structure. One such test is given by the ferential responses of the superficial cortical responses (SCR) evoked by stim-ating the cerebral and cerebellar cortical surfaces (FIGURE 2). Three pharma-logical agents of widely different chemical character all have identical effects the respective responses of each cortex. In all cases the cerebral SCR is gmented, while the cerebellar is unaffected.

The actions of the three drugs can hardly be ascribed to a uniformly "del-rious" effect on the cortical cells, especially since the augmenting effects are

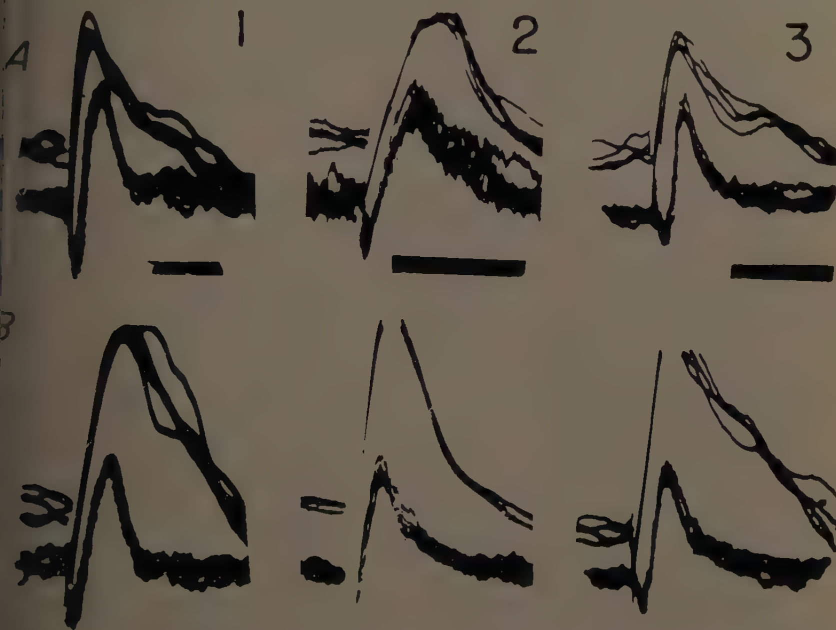

FIGURE 2. The similar effects of diverse drugs, as shown in simultaneous recordings of Rs from the cerebral cortex (the upper set of four superimposed traces) and the cerebellar tex (the lower set). *A* shows the controls and *B* indicates the reactions after (1) the topical plication of strychnine; (2) the injection of *d*-tubocurarine into the heavily heparinized imal; and (3) the topical application of creatine. In all three experiments the cerebral SCR s augmented, while the cerebellar SCR was changed only minimally. Time calibrations: msec. Reproduced by permission from *Inhibition in the Nervous System and γ-Amino-yric Acid* (Grundfest, 1960).

oduced in only one structure and are reversible. Deleterious effects are also led out when, as in FIGURE 3, a given drug has different actions on the poten-ls evoked in a single cortical system by different modes of excitation. These ects are characteristic for specific types of responses.

Our experiments have indicated further that the potentials of the evoked ponses, and even of "spontaneous" electrocortical activity, are largely .p.s (FIGURES 4 and 5), which are generated in the dendrites of cortical neu-ns. Furthermore, our data indicate that activity evoked in different cortical ions or even in the same region by different modes of stimulation differ in the ative amounts of excitatory depolarizing and inhibitory hyperpolarizing

p.s.p.s, as well, of course, as in the amounts of afferent and efferent spike activiti (FIGURE 6).

It is now well established that the laws governing the transmissional electrica activity of synaptic membranes are basically different from those of conductil

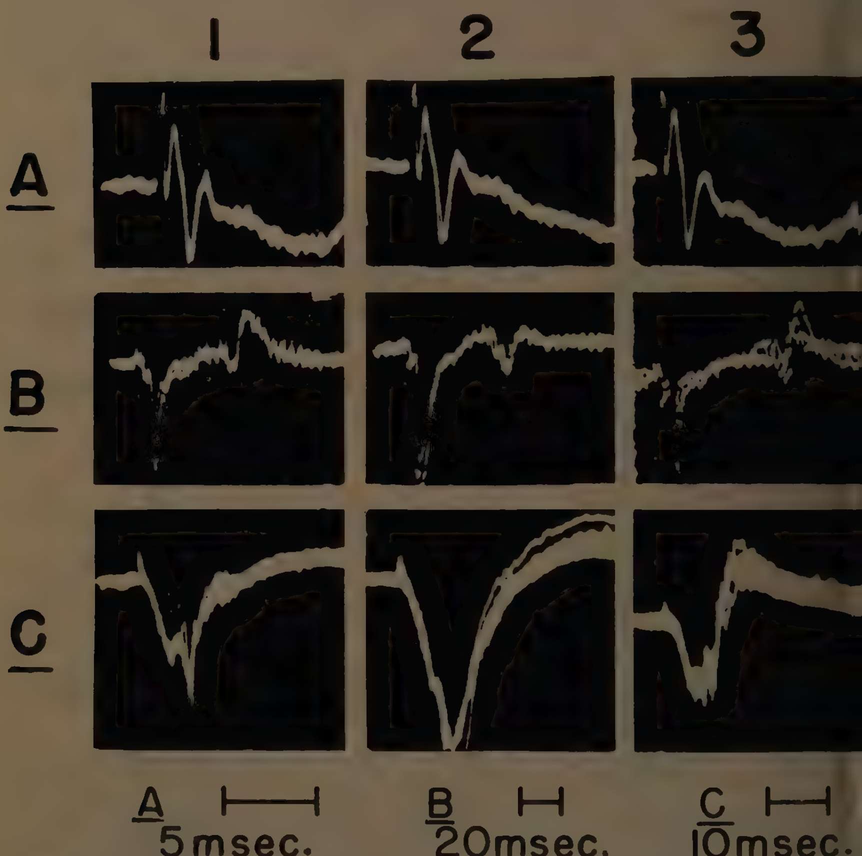

FIGURE 3. The effects of GABA and C_6 on the responses evoked in the paramedian lobu by different pathways of stimulation. *A* to *C* represent three different neuraxially inta succinylcholine-paralyzed preparations. Note the different time scales of the recordin In each experiment the records of column 1 show control responses, the records of column show responses after the application of GABA (1 per cent), and the records of column 3 sho responses after the application of C_6. *A* is the stimulation of the contralateral inferior oliv *B* shows the paired stimuli delivered to the contralateral midpontine reticular formation; a *C* indicates stimulation of the contralateral posterior sigmoid gyrus. Reproduced by pe mission from *The Journal of General Physiology* (Purpura *et al.*, 1959*a*).

spike activity of cell bodies and axons (Grundfest, 1957, 1958*b*, 1959*a*). Th on the basis of theoretical considerations alone it is therefore possible to set ce tain criteria for predicting and interpreting the degree and significance of ele trocortical activity.

P.s.p.s have a fundamental property: they are generated in electrically i

·citable membrane (Grundfest, 1957, 1959*a*). Accordingly they cannot ·opagate themselves by the local circuit excitation that operates in spike- ·nerating conductile membrane. P.s.p.s therefore are "standing" nonpropa- ·ted activity. Examples of extraordinarily localized responses that appear · be due to p.s.p.s have been reported by numerous observers (FIGURE 7).

FIGURE 4. I: *A* is the blockade of dendritic superficial cortical response (SCR) evoked by ·mulation of the cortical surface. The bipolar stimulating electrodes were about 1.0 mm. ·ay from the recording lead on the anterior suprasylvian gyrus. The indifferent electrode ·s in subcortical white matter. The initial response **1** is entirely surface negative, arising ·om the shock artifact; **2** is the response 50 sec. after the injection of 3.0 mg./kg. of *d*-tubo- ·rarine into the femoral vein; **3** is 20 sec. later; **4** is 5 min. later; and **5** is the response 20 ·n. later. The horizontal bar represents 20 msec. *B* is the electrical inexcitability of the ·naptically blockaded dendritic response. The stimuli were applied 0.8 mm. below the cor- ·al surface in the anterior sigmoid gyrus and the recording lead was on the surface directly ·ove. The indifferent lead was applied on bone over the frontal sinus. The initial response ·s a positive deflection, followed by dendritic negativity; **2** is the response 45 sec. after the ·ection of 2.0 mg./kg. of *d*-tubocurarine, showing that only the positive component re- ·ained; and **3** shows recovery after 90 sec. The horizontal bar represents 20 msec. *C* shows · direct and synaptic components of the antidromic and orthodromic activity in the pyram- ·l system. Records **1**, **2**, and **3** are responses at the cortical surface to stimulating the ·ramidal tract in the medulla. The indifferent electrode was applied to the frontal sinus. ·cords **4**, **5**, and **6** represent activity in the tract on stimulating the cortex. Records **1** and ·re initial responses; **2** and **5** show responses 5 min. after the injection of 3.0 mg./kg. of ·ubocurarine; and **3** and **6** show responses 20 min. later. The horizontal bar represents 10 ·ec. for records **4**, **5**, and **6**.

II: The blockading effects of *d*-tubocurarine on the surface-negative dendritic responses ·ked 2 mm. and 5 to 6 mm. from the stimulated site. The "near" responses are shown at ·; the "far" responses are shown at the right. Within 15 sec. after the intravenous adminis- ·tion of 3.3 mg./kg. of *d*-tubocurarine, both responses are reduced, and they are nearly ·olished after 92 sec. Recovery is virtually complete after 13 min. Composite figure from ·rpura and Grundfest (1956) and Fan and Feng (1957); reproduced by permission from *In- ·national Review of Neurobiology* (Purpura, 1959).

Despite the confidence expressed by some workers in the theory of volum conduction (cf. Elliott and Jasper, 1959), the theoretical basis of its applicatio to study of the brain is unsound (Lorente de Nó, 1939, 1953; Grundfest, 1960

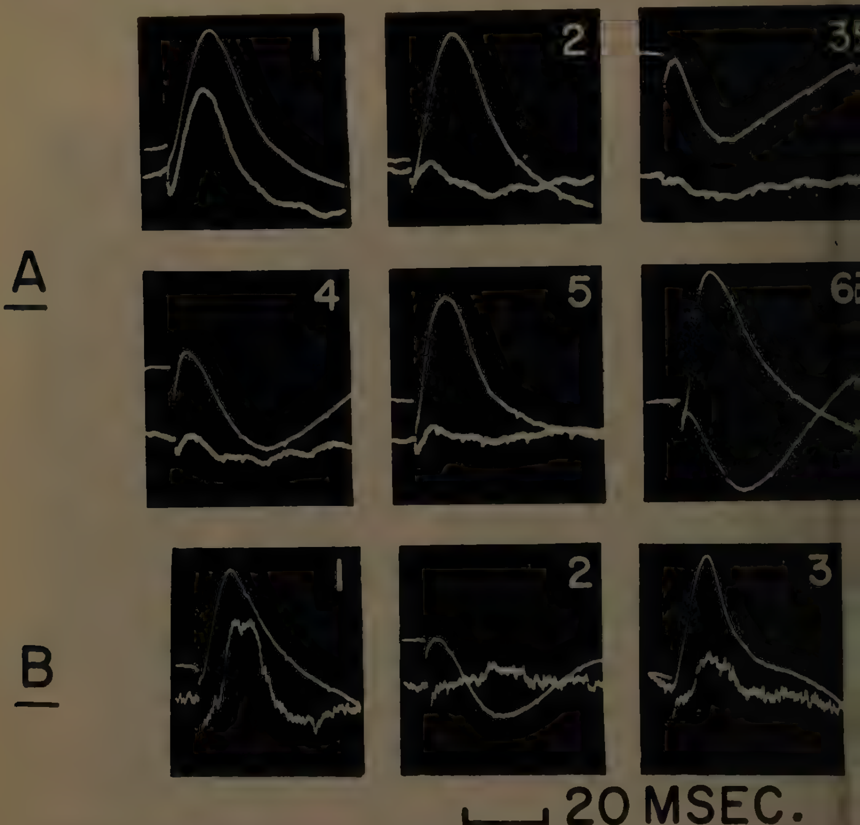

FIGURE 5. The restricted action of GABA on the superficial dendritic synapses of t cortex.

A: Simultaneous recordings **1** to **5** with large surface electrodes (*upper trace*) and small (1 μ) probe electrode (*lower trace*) of the SCRs of the cerebral cortex. The probe was on t surface in **1** and about 0.4 mm. below the surface in **2** to **5**. This region was approximate isoelectric with respect to an indifferent lead, and remained that way despite the large chang in surface potential produced in response to topical application of GABA (**3**). The beginni of recovery is shown in **4** and full recovery after the removal of the amino acid is represent in **5**. The extent of the shift in surface potential is shown in the superimposed records of

B: Differential actions of GABA on the cerebral and cerebellar SCRs. The simultaneo recordings show (*top trace*) the cerebral SCR and (*lower trace*) the simultaneously evoked ce bellar SCR **1** before, **2** during the action of topically applied GABA, and **3** during washi out of the GABA. Note the inversion of the cerebral SCR and elimination of the cerebell SCR. Reproduced by permission from *The Journal of Neurochemistry* (Purpura *et al.*, 1959

The disappointment of experienced physiologists in the data of depth recordi also stems from the realities of the characteristic properties of p.s.p.s. In FI URE 8 are shown two types of cortical responses, the SCR and the transcallos response (TCR), both as recorded from the surface and as explored with dep recordings. Neither obeys the "rules" of volume conductor theory, but f

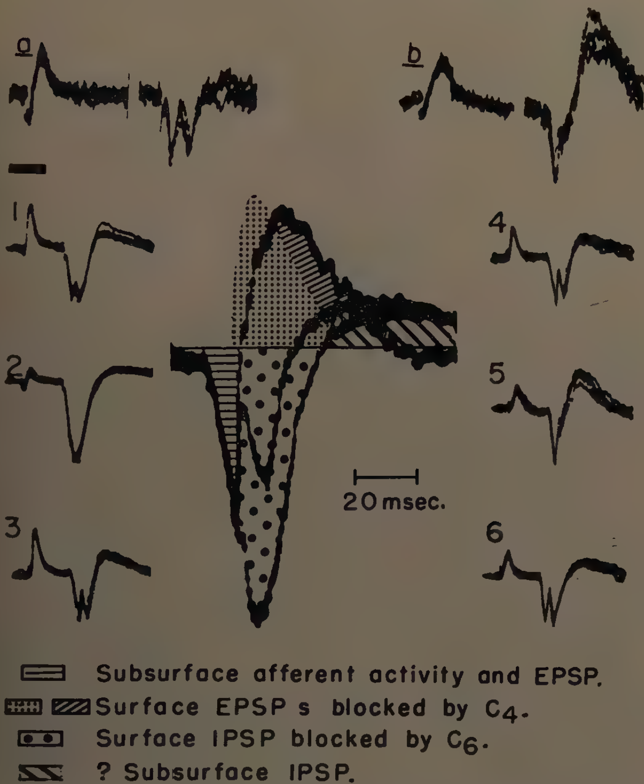

FIGURE 6. An analysis of different pharmacological effects on different responses in one ortical region. The paramedian lobule of the cerebellum in *a* and *b* is shown with the effects topically applied strychnine (0.1 per cent solution). Effects of GABA are shown in **1**, **2**, nd **3**; the effects of C_6 are shown in **4**, **5**, and **6**. Both of the latter agents were applied in 1 er cent solutions.

Two cortical responses are shown in each record: the first is a predominantly surface-negave SCR evoked by stimulating the paramedian lobule; the second is a cerebro-cerebellar sponses produced by stimulating the contralateral pericruciate cortex. This activity is mposed of two surface-positive elevations, shown in *a*, **1**, and **4**. Strychnine (*b*) and C_6 (**5**) d not affect the SCR, but they eliminated the second positivity of the cerebro-cerebellar sponse and brought out a large surface-negative potential. GABA eliminated the SCR (**2**), aving behind a small diphasic component of action potentials. The cerebro-cerebellar reonse was augmented by the growth of its second positive component. The reversibility these effects is shown in **3** and **6** about 15 min. after washing out the amino acids. The CR of the paramedian lobule is thus shown to be composed chiefly of surface-negative axondritic e.p.s.p.s. An analysis of the cerebro-cerebellar response is shown in the inset *nter*), in which records **2**, **4**, and **5** are superimposed. An early positivity and, perhaps, e small negativity represent subsurface activity that is not affected by the amino acid drugs. large component of the surface positivity ascribed to the axodendritic i.p.s.p.s (*large dots*) characteristic of the paramedian lobule and is disclosed by application of GABA. Blocke by C_6 reveals a smaller, normally obscured surface negativity (*small dots*) and an addinal component of axodendritic e.p.s.p.s (*closely spaced diagonals*) elicited by the stimulus the absence of the i.p.s.p.s. The time scale at the upper left is 20 msec. for the experiment *a* and *b*; it is 40 msec. for the experiments in records **1** to **6**. Reproduced by permission om *The Journal of Nervous and Mental Disease* (Grundfest, 1959*b*).

different reasons. The SCR evoked by employing weak stimuli to the surfa is due to p.s.p.s confined to the superficial 0.4 or 0.5 mm. of cortex. Thus whe the depth-exploring electrode was inserted below this superficial layer it d not record any change in potential. The TCR, on the other hand, is formed l activity of depolarizing and hyperpolarizing p.s.p.s complexly distributed the depth of the cortex. The recorded potentials accordingly vary dependi upon the local distribution of the different activites. Evidence for these co clusions is provided by the behavior of these two responses when challenged l gamma-aminobutyric acid (GABA).

This drug blocks selectively the axodendritic excitatory, depolarizing p.s.p (Purpura *et al.*, 1957, 1959*b*). The SCR is then modified to a surface positivi

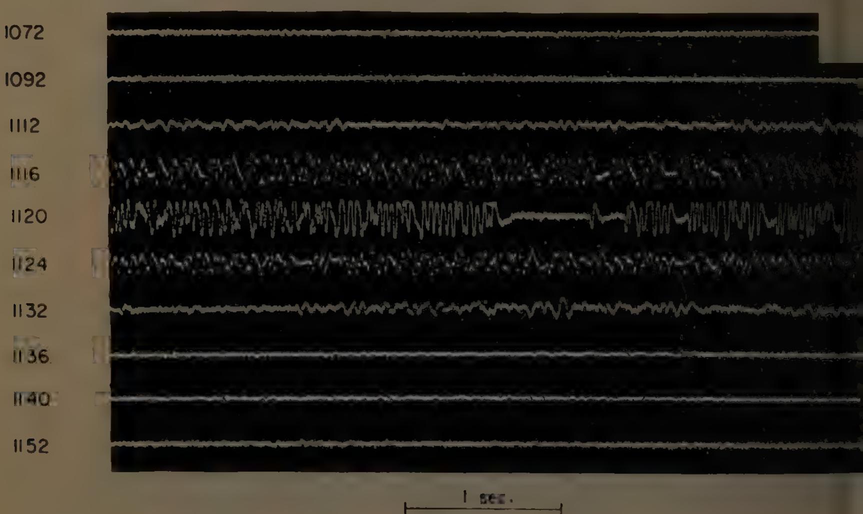

FIGURE 7. Spontaneous slow wave activity localized within less than 20 μ in the cortic depth. Each line shows the potentials recorded with a 4-μ microelectrode at the depth (microns) indicated at the left. Between 1112 μ and 1132 μ there was a region of intense a tivity, with relatively quiescent cortex areas above and below it. Reproduced by permissi from *The Journal of Neurophysiology* (Mountcastle *et al.*, 1957).

representing the remaining axodendritic activity, that of inhibitory surfa positive p.s.p.s. The depth recordings then show that the initial distribution p.s.p.s remains, but is now positive instead of negative (FIGURE 9). On appl ing the same drug to modify the TCR, however, the distribution in depth of t latter response is markedly modified. As is to be expected from the abo analysis, a mirror-image potential that was absent before GABA was appli now appears in the depth (FIGURE 10). This is more truly a case of volum conductor recording in experimental circumstances in which perturbing pote tials, excitatory, surface-negative axodendritic p.s.p.s of the cortical surfa were eliminated, while the deeper-lying generators were unaffected.

With these data as the background we may now revert to the main proble The potentials recorded from cortical surfaces or from the cortical depths are complex mixture of nonpropagated p.s.p.s and of conductile spike activity, b

edominantly of the former. P.s.p.s, however, are a special form of activity, e preliminary to an executive, all-or-none action mediated by spikes. A mple example may clarify this distinction. Suppose we were capable of ading the endplate potential of a single muscle fiber in infinite degree, for stance by appropriate applications of *d*-tubocurarine. In such a situation e might send in many impulses from the motor axon, each producing an

FIGURE 8. Potentials recorded in the cerebral cortical depths in correlation with the erficial cortical response (the SCR), at *A*, and the transcallosally evoked response (the R) at *B*. Simultaneous recordings were made from the surface (*upper trace*) and from an loring microelectrode (less than 10 μ) at the indicated depths below the surface. A sucylcholine-paralyzed preparation was used, with a suprasylvian gyrus recording. The ativity is upward in these records. The insert shows the time and amplitude calibration: cycles/sec. and 300 μv. Reproduced by permission from *Electroencephalography and nical Neurophysiology* (Purpura *et al.*, 1960).

endplate potential (e.p.p., or p.s.p. in the generalized terminology; cf. Grundfest, 1959*a*). There would then be a region with localized activity of p.s.p.s but the muscle fiber would not respond with its executive functions, a spike and contraction.

FIGURE 9. The surface (*upper trace*) and subsurface (*lower trace*) potentials during the superficial cortical response (SCR), before and after application of 1 per cent GABA to the surface. The tip of the saline-filled exploring microelectrode was less than 10 μ. The approximate subsurface depth is indicated on the left in microns (μ). The calibrations are as in FIGURE 8. Note that below a depth of about 400 μ there were no significant potentials to reflect the large surface-negative or surface-positive SCRs. Reproduced by permission from *Electroencephalography and Clinical Neurophysiology* (Purpura *et al.*, 1960).

This distinction between the characteristically different potentials is espe-ially sharp in the brain. The potentials that are recorded in the brain are omplex resultants of activity of different signs, with different spatial and emporal orientations, each succeeding activity conditioned by the preceding ne to various degrees. Not only is the number of synaptic connections much arger than is that of axons and cell bodies, but the number of nerve fibers ntering and going out of the brain case is relatively very restricted. Thus the

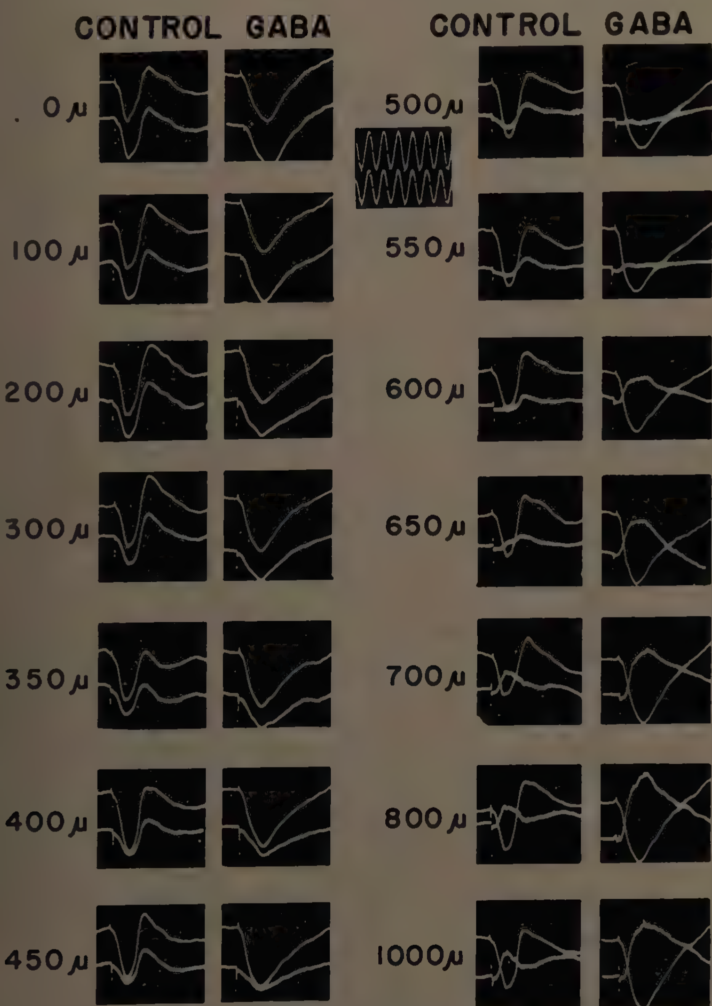

FIGURE 10. A series of recordings, similar to those in FIGURE 9, for the transcallosal cor-cal response (TCR). The large surface positivity in the control records was not reflected a deep negativity of comparable magnitude. However the augmented surface positivity ter GABA administration was accompanied by the appearance of a correspondingly large ep negativity. Reproduced by permission from *Electroencephalography and Clinical Neuro-ysiology* (Purpura *et al.*, 1960).

messenger properties of bringing information and of carrying out executi decisions based on that information are restricted to a small afferent input a to output of spikes in a relatively small number of neurons. The vast propo tion of the neuronal activity, in the form both of synaptic events and of c discharges, is hidden from sight, even more than is the ice hidden below t surface of an iceberg. Indeed the electrocortical potentials that do appear m result from quite different types of activity, so that even their similar appe ance need not indicate physiological or pharmacological relationships (Sigg a Grundfest, 1959).

If the above interpretation is valid, then a searching re-examination mu follow regarding the significance of recorded electrocortical data, which c mean a great deal in one context and be almost meaningless in another. T rethinking is admittedly difficult,* but the realities of the brain as an ext ordinarily complex synaptic organization of neurons demand such re-exami tion.

However, not only re-examination and new modes of interpreting old ty of data are required. Perhaps of even more importance is the need for n criteria of desirable data, and for new methods to obtain such data. No long is it adequate merely to compare size or form of potentials; the potentials mu be dissected and subjected to experimental scrutiny with all available tools, cluding those of pharmacology. A single experimental variable, as for exam the use of one drug (cf. Mahnke and Ward, 1960; Elliott and Jasper, 1959) not enough to provide adequate information about electrocortical activity, a more than a single equation can solve for a function with several variables. N can the inadequate analysis of the mode of action of drugs still found in textbooks (cf. Goodman and Gilman, 1955; Drill, 1958) provide useful gu posts.

So complex an experimental material as the brain lends itself all too read to descriptions such as "fatigue," "refractoriness," "irradiation," "releas and numerous other verbalizations that pass for explanations of mechanism However it will come as no surprise to our Soviet colleagues that quantity a quality are inextricably intertwined in the operation of the central nerv system. Weak and strong stimuli produce responses that differ not merely size. Even an apparently negative act, inhibition, can lead to an increase activity or to the introduction of newly appearing activity previously su pressed. Thus history, too, becomes an actor in the complex play of neuro

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* An observation by the eminent historian and Master of Peterhouse, H. Butterfield (19 is particularly relevant here. He says: ". . . of all the forms of mental activity, the n difficult to induce, even in the minds of the young who may be presumed not to have lost t flexibility, is the act of handling the same bundle of data as before, but placing them in a system of relations with one another, by giving them a different framework. . . ." (page 1

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DISCUSSION: PART I

Karl Pribram (*Departments of Psychiatry and Psychology, Stanford Unive sity Medical Center, Palo Alto, Calif.*): The wonderful experiment Miller has to us about was undertaken to show something about the nature of the ra "drive" for water; it has proved that when rats are not deprived of water th do not lick. This is such an excellent demonstration of our divergence of vie points: it seems that rats are smarter than people under certain circumstanc Why should they lick when they are not thirsty?

Miller has also brought up very nicely, although perhaps inadvertently, t work of Harlow and his associates referring to "curiosity;" thus to the conce that reinforcement can be thought of in terms other than drive, if drive is d fined in terms of physiological processes that deal with the regulation of wat and food intake.

To turn to Magoun's presentation: as heretofore, he has simplified o world for us and stated that those of us in the West believe one thing wh those of us in the Soviet Union believe something else. I want to addre myself to this idea.

As I understand it, the work of Morrell was taken to show that closure conditional reflex behavior is dependent on a cortical mechanism.

Magoun also stated that the model proposed by Sokolov suggests that pa of the brain other than the cortex are involved in the matter of making t "temporary connections." Let me adduce some Western evidence in supp of this. Let us think for the moment of the brain as really being made up two brains. One brain is the "classic" brain we learned about in school: t posterior-lateral surface of the cerebral cortex and the ascending and descen ing paths from this that course up and down the neuraxis. This is the pa of the brain that contains Pavlov's "analyzers" and is the part that deals wi the transmission and processing of information.

The "other brain" we might call "Magoun's brain," because he has co tributed so much fundamental work to its discovery. This "brain" mak up the core of the central nervous system. It has a rostral extension into t forebrain: the medial and basal limbic cerebral areas and, additionally, t frontal eugranular isocortex.

We have made ablations and irritative lesions in the classic brain, the po terior-lateral parts of the isocortex. Such lesions severely disturb the abili of monkeys to make differentiations. If a monkey has been trained prior an ablation of the cortex he is no longer able to make the differentiations aft the ablation. He fails to make the appropriate choices even though he h mastered them preoperatively. On the other hand, if "irritative" (alumin hydroxide) lesions are made, such performances remain intact. However su irritative lesions have another effect. The *learning* of differential responses retarded about fivefold.

An entirely different sort of process seems to be impaired when lesions a made in the limbic portions of the "core-brain." Train a group of norm monkeys to differentiate between two grays; then test them in a situation which the darker of the two grays, which has been rewarded during traini now becomes the lighter of a new pair. The normal monkeys will uniform

transpose this response to the darker of the new pair in the test situation. In other words, they will take the relation, "the darker of two" that they had learned during the training sessions and transpose this experience to the new situation.

Monkeys with "core-brain" lesions—bilateral removals of the amygdala—behave very differently in this task. Whereas the normal animals perform the test trials as if nothing had been changed, monkeys with amygdala lesions stop short the moment the test stimuli are produced. These monkeys act as if the test grays were "novel": they respond on a 50:50 basis, as if they were in a totally new situation. They do not transpose their responses from what they had learned to the new situation.

This is one of a series of experiments that raises the question: Is the core brain critically involved in Pavlovian generalization? The experiments of E. Roy John and Keith Killams, which Magoun quoted, show that, during orientation, neural activity in many parts of the brain can be correlated with a labeled input; that as habituation progresses a restriction of the correlated neural activity takes place in the core systems.

It seems, therefore, that both the electrophysiological and the behavioral evidence lead to the conclusion that the core systems have something to do with a process that has some semblance to that postulated by Pavlov and called by him "generalization."

The classic posterior-lateral systems, on the other hand, seem to deal with something quite different: differentiation, analysis, in the terms Pavlov used. When a lesion is made in these classic systems the organism reacts normally to any one cue on the basis of its prior experience; only when choices are to be made, only when choices between different objects have to be made, does the deficiency in behavior become manifest.

The burden of my argument is that the "closure" of the conditional reflex does not take place transcortically. In this argument, East and West are beginning to agree. The core systems seem to be as vitally concerned as the classic brain. Only by the interaction of these "two brains" can learning take place. The specification of the details of this interaction is our common task during this next decade.

Robert Galambos (*Department of Neurophysiology, Walter Reed Army Institute of Research, Washington, D. C.*): In connection with Pribram's comments contrasting the classic lemniscal brain (the analyzer systems of Pavlov) with the core brain (the reticular system of Magoun and his colleagues), I propose to report an experiment from our laboratory recently described elsewhere.[1] This study was designed to reveal the separate contributions of the lemniscal and the reticular systems to the cortical electrical response evoked from awake cats by click stimuli. Our plan was to record—in the unanesthetized animal from electrodes permanently implanted upon the auditory cortical area—the activity aroused before and after an operative lesion that destroyed the classic lemniscal tract. Our expectation was that the electrical activity produced some days *after* cutting the brachium of the inferior colliculus would surely differ from that recorded prior to the operation; the results show, however, that in so far as our present techniques permit, no significant difference between the two can be discovered in their latency, wave shape, and duration.

Successful interruption of the classic pathway was established during life demonstrating the absence of click-evoked cortical response with the under barbiturate anesthesia and, after death, by examination of histologi preparations of the brain.

These results raise several points of interest. Most of us conceive, I suppo of the classic lemniscal system as providing the speedy and specific route which cochlear excitation spreads to the cortex. In these operated anim (unanesthetized), however, speedy conduction still exists with the clas pathway interrupted, and thus some alternate mechanism for the rapid c duction must be visualized as operating in both the normal and the opera state. This alternate route, furthermore, can by itself arouse in the cor the electrical response we presently visualize as arising at least in part fr the influx via the classic auditory pathway. The data suggest in brief t the so-called core system in the brain performs still more of the functi tacitly attributed over the years to the classic (or analyzer) systems.

This brings me to my final point: If the heavy-fibered classic auditory pa way is not required for rapid dissemination of auditory information to cortex and if, in its absence, a normal electrical response can be provok there, what unique property may we assign to this massive and obviously portant collection of fibers?

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H. W. Magoun: I have been fascinated by these comments, both for th content and because they have been so revealing of the interests and poi of view of each of the three discussants.

With his customary quizzical questioning, Neal Miller commenced with exploration of the significance of alterations of electrical activity recor from the brain during the learning process. As he himself remarked, th stages can be compared with stages in the establishment of learned behavi During the formation of a conditioned response, there can be identified initial phase of generalization, followed by a phase of concentration or dif entiation. During the initial period of training, electrical responses evo in the brain by afferent stimuli are distributed widely both in the cortex in deeper structures. When learned behavior is established, however, s responses become much more concentrated and ultimately are limited to cortical area for the unconditioned signal. These features of initial generali tion and subsequent concentration, matching those of the learning pro itself, certainly suggest a significance for the alterations in the electrical tivity of the brain during learning.

Such an analogy is not of binding relevance, however, and efforts are n beginning to be made to verify the significance of these electrical alterati more directly. It is perfectly feasible technically to implant electrodes int region of the cortex or deeper part of the brain and to stimulate or record fr

such regions over long periods of time. Work has begun in Los Angeles to examine the features of local responses evoked both in the cerebral cortex and in the hippocampus during stages of conditional learning. By determination of the threshold, latency, amplitude, and recovery time of such responses, it is possible to obtain a direct and independent monitor of the excitability of brain regions. It is hoped that in this way it may be possible to investigate modifications of the excitability of different regions of the brain that have been proposed or inferred to occur during stages of the learning process.

The balance of Miller's remarks have dealt, as might be expected from his interests, with factors of drive and motivation and with the physiology of the unconditioned reflex in the learning process. Miller has himself contributed significantly to this field, as have his colleagues in physiological psychology, particularly James Olds. From their studies it now seems possible to identify major reinforcement mechanisms in the brain and to distinguish two categories of them, one for positive and the second for negative reinforcement of behavior. These reinforcement mechanisms have been found to be distributed in the cephalic end of the brain stem and in the ring of limbic structures bordering its attachment to the hemispheres. These are the mechanisms that have been laid down very early in the process of evolution to preserve the life of the individual and the survival of the race. They form the very core of the unconditioned reflex mechanism.

The initial interest of the Pavlovian school in the importance of the cerebral cortex in the conditional reflex diverted investigative attention from these deep-lying brain mechanisms, the existence and importance of which was recognized and acknowledged, however, both by Pavlov and by many of his associates. In the West, the activities of the Yale school, to which the late John Fulton himself contributed so much drive, called increasing attention to this limbic system, following the earlier anatomical studies of James W. Papez and, before him, of Paul Broca. Today the valuable role that the limbic system plays in all these activities is widely recognized. Most recently, characteristic patterns of electrical activity, the hippocampal theta rhythm and the 40/sec. bursts from the amygdala, have provided a novel means of studying limbic function and of relating it to behavior.

With his customary faculty for making broad and significant syntheses out of diverse bodies of data, Karl Pribram has brought clearly before us the distinctions between the classic, lateral neural mechanisms, the Pavlovian analyzers, which serve the information-handling and discriminative functions of the brain, with which we all began our education; and the core mechanisms comprising the lower reticular and higher diencephalic and limbic systems, which have been more recently elaborated. Pribram's suggestion that the core systems subserve the Pavlovian stage of generalization while the classic lateral mechanisms are more concerned with the functions of analysis, discrimination, and differentiation, is an exceedingly intriguing proposal and one that should stimulate a great deal of study.

These classic functions of analysis, discrimination, and differentiation seem to require aspects of neural performance implicit in the concepts, initiated more by A. A. Ukhtomsky and N. I. Vedensky than by Pavlov, of the role of a

dominant focus in the learning process. While we are just beginning, from translation of Ukhtomsky's papers into English, to understand the basis of his proposal, I gather that he conceives within a dominant focus a central core of excitation, with a second essential component feature consisting of an inhibitory surround.

There is thus involved in these functions the active role of inhibition in effecting what Pribram has called the falling-out of components. The study of inhibitory mechanisms in the classic or lateral neural systems has been initiated within the past few years by study of sensory control mechanisms and corticoreticular systems of the brain. A collection of negative feedbacks seems to be emerging from these studies in what must certainly be one of the most fruitful products of the application of cybernetic principles to an understanding of the nervous system. One of the most attractive areas for future study would seem to lie in exploration of the interrelations and interactions of these core systems and the classic lateral mechanisms. Hopefully we may ultimately be able to determine in what manner these limbic and lower core mechanisms are able to modify the performance of the classic lateral mechanisms serving the functions of the Pavlovian analyzers and the information handling and discriminative activities of the brain.

Robert Galambos can be counted on, as always, to write about the auditory system, which is dear to his heart, and additionally to present with beautiful clarity the sequential stages of investigation that brings out new knowledge and makes one think about it. When he is unable to distinguish modification of a click-evoked response in the auditory cortex after bilateral section of what has previously been called the classic auditory pathway, except under conditions in which more of the brain is paralyzed with nembutal anesthesia, he can rightly ask what function does the classical pathway serve. As a long-standing protagonist of the core school of neurophysiology, I do not believe that I should be expected to try to answer his question.

P. K. Anokhin (*Academy of Medical Sciences of the Union of Soviet Socialist Republics, Moscow, U.S.S.R.*): I propose to make a few observations on the paper delivered by Magoun because our Soviet laboratories for many years have been investigating the correlation between reticular formations and higher nervous activity.

The first and most important question is that of the contribution of the reticular formation to the future development of the study of higher nervous activity. We have observed beyond all question, as the result of much work, that study of the reticular formations opens up many new areas in the field of higher nervous activity. Every significant school, if it has at its disposal sufficient data, uses certain already proved facts, such as that of the conditioned reflex; at the same time, it utilizes a great many hypotheses in its work and, from the point of view of the reticular formations that previously we did not understand very well, we now have been able to come to a new approach, a new method in attacking this problem.

I propose to discuss briefly the contribution of the study of reticular formations to the field of higher nervous activity.

First, reticular formations have shown that there are two channels by which the conditioned reflex flows. If one accepts the fact that today our concepts of higher nervous activity are based on the concept of a single channel, that is, the traditional classical conception of a single channel through which this process occurs, one realizes that with the introduction of the theory of two channels we will inevitably expand our knowledge of the influence of this particular factor on the localization of the conditioned reflex.

As a result of studies made from experiments in particular areas, we can conclude that a stimulus does act on the cortex of the cerebrum and does in fact produce a conditioned stimulus.

For us, in our particular laboratory, the principal enigma that we must solve is the following: we must try to determine what the conditioned reflex brings to the particular zone that it acts upon and what is the general stimulus that the conditioned reflex brings to the entire cortex as a whole. The cortex itself will receive a conditioned reflex.

Hence we have reached the following conclusion: the conditioned stimulus breaks down into a whole series of sectors having divergent and varying effects on the cortex. Consequently, the so-called Magoun system has raised the question as to what creative work can be done that would be based on the study of the individual excitations that appear in the cortex, that come into the cortex under the conditions of excitation.

The fact that this monograph begins with the paper by Magoun perhaps may be interpreted as a sign that this is the beginning of closer collaboration between the physiologists studying the higher nervous centers, that is the centers of higher nervous activity, and the neurologists, the neurophysiologists.

P. S. Kupalov (*Academy of Medical Sciences of the Union of Soviet Socialist Republics, Moscow, U.S.S.R.*): I started my studies with Pavlov 50 years ago. At that time investigations in the field of higher nervous activity were performed only in Pavlov's laboratories, and this was true for a long period of time. Now all is changed: so many people in all countries are working in this direction and the area of investigations has been so enlarged that it is difficult to know well or to understand adequately all the details of this research.

I must say, of course, that this is quite natural. The brain as a physiological organ is a very complex one, and there are many approaches for studying it. Whenever we think of the brain, therefore, we always think of the diverse, well-organized, and complex nervous processes that constitute the foundation of the work of the whole organ. At present, because of the investigations of many physiologists—chiefly those of the United States and, primarily, Magoun and his collaborators—we have a new approach that permits study of the functions of the constituent parts of the brain. I must confess that I have not followed carefully and systematically all the literature on this subject. I have read Magoun's book *The Waking Brain*,[1] but I have not yet had the time to compare and connect all of his new facts with our own findings. This situation shows only that the brain is a very complex organ and that we must do everything possible to graph how, in the final analysis, it will be seen and comprehended.

Perhaps workers in the United States sometimes find it difficult to understand

Soviet investigators quite correctly. One possible cause of this situation migh be that we workers in the Pavlov laboratory always thought about the brai very broadly, but we spoke about it in less expansive and schematic terms, a did Pavlov himself. Pavlov did not like to utter large generalizations that g far beyond the facts; sometimes he did not say in public what he thought i private. I can say that I knew two Pavlovs: one Pavlov in the laboratory, wh would say something very affirmatively and then vigorously defend it; and als another Pavlov at home, who, when he was asked the same question, would say "Oh yes. I've thought about it. I know that our conclusions are not quit true, that they do not combine *all* the facts but only those that seem most sig nificant. It is impossible to study them all together. One must close one eyes to the complexity of the question and study it gradually step by step."

There has been discussion in these pages—in Magoun's paper—about t orienting reflex. This is a complex phenomenon, and much that we know abou it comes from general observation. I shall briefly describe our new experiment

We have some cats in which we have cut all connections between thalamu and cortex; that is, we have gone through the parietal area of the cortex to t thalamus and then cut all connections between the two. These cats can wa and perform other motor functions, and they have well-pronounced orienti reflexes. It may also be said that the cat "sees," although we know histologi ally that vision is nonexistent. If a new sound stimulus is presented to one these cats while it is walking, the stimulus at once inhibits any motor activit the cat will stop and will stand still for some time turning its head toward t stimulus. It will then move toward the source of the sound. This same ph nomenon has also been seen with stimuli that act upon the sense of sme Therefore the orienting reflex and all other unconditioned reflexes apparent interact with each other continuously.

What then *is* the orienting reflex? There is need to analyze this reflex n only from the point of view of electric potentials but also in terms of these sir ple reactions.

One such cat, two days after its operation, had kittens. In general, her m ternal instinct seemed to be split in some respects. In response to skin stim lation the mother cat would lie in a position in which her kittens normally cou suck and would give similar simple responses to smell stimuli from her kittens she would lick them, for example—but she was incapable of complex matern behavior. She could abandon her kittens; because she could not coordina her functions with the needs of her kittens, they soon died.

We found it possible to establish in such a cat something like a condition reflex when we connected a sound stimulus and the presence of food. The were some movements and some excitation.

Galambos, I believe, will agree that this behavior, of course, means som thing. When these connections between the cortex and the underlying pa of the nervous system are cut, we find ourselves with quite a different anima

I greatly appreciated the papers and comments of Magoun and many othe I myself, about 25 or perhaps 20 years ago, found that in the brain there are t different mechanisms: one that responds to such stimuli as food and the nec sity of defense; and another mechanism that involves only some functio change of the brain, such as excitability, positive and negative.

I now find and appreciate the same reasoning in Magoun's paper. In *The Waking Brain* Magoun notes that the latter mechanism is what physiologists call the "arousal reaction." When I proposed this concept—which I called a reflex of changing and regulating the functional state of the brain—the idea was so new that I was not even understood by my colleagues in the Soviet Union. Later I termed this mechanism "the shortened or truncated reflex"—a name suggested by Razran—whose purpose or meaning was to change excitability and efficiency, to prepare the brain for further activity.

I was in a position 10 years ago that was not very pleasant for me, but now I see that all is changed and my advanced idea is accepted. I thank Magoun for his brilliant experiments, since he helps my arguments with his new facts. Now no one blames me for having propounded the concept of this mechanism.

Reference

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Part II. Cortico-Subcortical Interaction

INTRODUCTORY REMARKS

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It gives me particular personal pleasure to add my words of greeting to o Soviet colleagues and especially to my good friend P. K. Anokhin who, amo others, did so much to make my two visits to Moscow both rewarding and d lightful.

I shall take this occasion to repeat some remarks I made in January, 19 on my second visit to Moscow, at the Academy of Pegagogical Sciences and the Academy of Medical Sciences.

I said that I had long sought a common denominator that all mankind cou support. If, indeed, no such common and meaningful approach could be foun then indeed we might despair. First I had looked for such a common denon inator in religion and later in culture, but I soon realized that religious a cultural differences tended to divide rather than to unify the human race. had decided, therefore, that one must look for such a common denominator a more fundamental level, for instance in biology. Then it occurred to me th *parental concern for their very young* might serve as such a unifying concep This concept is well rooted in biology; it is present in nearly every species, a can be traced in evolution as far back as the insects. In fact, few species animals can survive without exhibiting special protective behavior for the su vival of their offspring. In man the parental concern for children is not on the center of family life, but is also one of the mainsprings for the high human aspirations.

I then pointed out that we have reached a point in history at which, for t first time, no nation, however strong, is powerful enough to protect its ov children and to guarantee the survival of that which is our most precious poss sion: our children and our children's children. For if the nuclear bombs con New York will go *pouf*, London will go *pouf*, and even Moscow might go *po* I stated, however, that I believed that there was a way in which the survival our children could be guaranteed. If the nations would join hands to prot each other's children—if the Union of Soviet Socialist Republics would prot American children and if the United States of America would protect the Sov children—then all children would be protected.

I am happy to have the opportunity to repeat these remarks here in the pa of the *Pavlovian Conference on Higher Nervous Activity*. I can also tell you th both at the Academy of Medical Sciences and at the Academy of Pedagogi Sciences my suggestion evoked a most encouraging and ethusiastic respon I believe, therefore, that concern for the survival of our children and of children, and the necessity for joint action for this purpose, forms a sound ba for cooperation and for friendship among all the peoples of the world.

ELECTROENCEPHALOGRAPHIC ANALYSIS OF CORTICO-SUBCORTICAL RELATIONS IN POSITIVE AND NEGATIVE CONDITIONED REACTIONS

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The past decade has been marked by a stormy development of neurophysiological research in the subcortical structures of the brain. It is generally recognized that the experiments of Magoun, Moruzzi, Bremer, Grundfest, Forbes, Morison, Bishop, and many others (Moruzzi and Magoun, 1949; Grundfest, 1958; Bremer, 1938; Forbes and Morison, 1939; Bishop, 1936) served as the impulse for this extensive research. At the same time, all of the aforesaid research was made possible by the parallel development of electronic and stereotaxic techniques that enable investigators to analyze the processes of excitation in any of the finest nervous structures, regardless of their location, in the depths of the brain.

It was precisely this improvement in research techniques that made it possible to work out in detail the physiological characteristics of the reticular formations of the brain stem and the thalamus, which now constitutes an independent and very fruitful trend in general physiology of the nervous system (Magoun, 1950; Jasper, 1954).

It is perfectly obvious that this development of the general physiology of the cortex and the subcortical structures of the brain inevitably had to come in contact with the powerful school of physiology that, for one half of a century, has also been studying the general physiology of the brain, although it has been following entirely original paths and using an original method, the method of conditioned reflexes. I am referring to the school of I. P. Pavlov, whose pupil I have had the fortune to be.

It would be hard to name an international symposium on the mechanisms of the brain at which the mechanism of the conditioned reflex was not the pivotal point of discussion. This is natural. In any fine analytical investigation of the cortex and the subcortical structures the conditioned reflex is the integral act of behavior, against the background of which the cognitive value of any such analytical investigation is revealed.

This is particularly true of the study of cortico-subcortical relationships, which is becoming the central point for this new period in the development of neurophysiology and, at the same time, forms the basis for understanding the conditioned reflex activity of animals and man. It is precisely at this point that the interests of general physiology of the brain come into closest contact with the interests of physiology of higher nervous activity.

The special and important role of the subcortical apparatus for conditioned reflex activity was noted by Pavlov. On the basis of numerous experiments conducted in his laboratory he arrived at the conclusion that, although subcortical activity was inert, it was nevertheless strong in its energy potential and represented a kind of "blind force" that ensured a high energy level for the functional interactions among the cortical elements. This evaluation of

the role played by the subcortical apparatus was expressed with particul clarity in his physiological analysis of hysteria (Pavlov, 1938). Pavlov's la oratories also established a reverse influence, that is, an influence exerted l the cortex on the subcortical apparatus, with a special stress on the "restrai ing" and "regulating" influence of the cortex on the emotional behavior of an mals and man (Pavlov, 1938).

All of these propositions were expressed long before investigation of t general physiology of the nervous system resulted in the discovery and explan tion of the "ascending nonspecific activating effect" of the reticular system the brain stem and thalamus on the cerebral cortex.

Now that we have very fine electronic instruments and extensive informati on the physiology of the subcortical structures, we can really marvel th Pavlov, who in his time had very insignificant information on neurophysiolog could foretell with surprising exactness the general purport and role of su cortical functions in the organization of the process of higher nervous activit

It is natural, however, that at that time Pavlov's laboratory was unable show precisely which concrete subcortical structures were involved in the d ferent forms and different stages of higher nervous activity, by what mec nisms these subcortical structures exercised their influence on the cereb cortex, and precisely to which cortical layers and cell elements this effect spre

The elucidation of these last questions constitutes a recent achieveme This branch of neurophysiology is being elaborated with extraordinary int sity, and extensive material has already been accumulated in this field.

Precisely these achievements of neurophysiology inevitably gave rise to t question of correlation between the latest achievements of neurophysiology a the results of research in the mechanisms of higher nervous activity by t conditioned reflex method.

The present report is a modest attempt to collate, on the one hand, t achievements of modern neurophysiology and, on the other hand, some of t basic problems of higher nervous activity. I propose to make this collation the basis of a synthesis of already available data and by an analysis of t special combined experiments conducted by my colleagues and myself in laboratory.

I shall begin my narrative with the formulation of some perfectly obvio contradictions now arising between the basic ideas of modern instrumen neurophysiology and the physiology of higher nervous activity.

It is precisely these contradictions that served for us as the point of depart in conducting many electrophysiological experiments, to the results of whic now call your attention.

The main contradiction is in the understanding of the essence of the ascen ing nonspecific activating effect of the reticular formations of the stem a thalamus on the cerebral cortex, so brilliantly elaborated in the laboratory Magoun and his followers.

The generally accepted interpretation of this phenomenon assumes that t effect is generalized throughout the entire cortex and probably all the corti cellular elements. *Desynchronization*, that is, transformation of low-frequen high-amplitude electrical activity into low-amplitude, high-frequency electri

activity, is usually regarded as the electrophysiological expression of this generalized activation.

As is well known, in direct stimulation of the brain stem reticular formation, as well as in sufficiently strong stimulation, for example, of the sciatic nerve, such activity spreads through all the regions of the cerebral cortex. It is tacitly assumed that this activity concerns all the cell elements of the cortex, hence, its designation as "diffuse" activity.

Despite the fact that this point of view is the most widespread and the term "nonspecific" is the only one applied to the activity of the reticular system of the brain, certain doubts as to the application of the epithet "nonspecific" to the activity of the subcortical reticular formations have, in recent years, arisen repeatedly.

Thus, for example, in describing the functional characteristics of the thalamic reticular formations, Jasper writes: ". . . . The nonspecific system is actually a very specific system with peculiar properties which distinguish it from the other systems. It is diffuse only in so far as it spreads, since it overlaps all the projections from the specific systems. Nevertheless, in the thalamus this system is a very specific complex of neurons which is diffusely distributed over the thalamus" (Jasper, 1954).

Jasper's experiments with simultaneous recording from several individual cortical neurons and correlation of the activity of these individual neurons with the electroencephalogram confirmed these assumptions (Jasper, 1958).

Purpura, in his very recent article on the nature of electrical potentials, concurred with this opinion in examining the characteristics of the synaptic organizations on cortical neurons, and advanced the concept that there are special "synaptic organizations" in the cortex for each complex of afferent influences (Purpura, 1959).

Since 1955 our laboratory has obtained a series of experimental results that convince us that the idea of "nonspecific activation" in its generally accepted interpretation cannot be applied to the analysis of the processes of higher nervous activity. I shall set forth below the considerations that brought me to this conclusion.

The basic law governing the formation of conditioned reflex activity is the law of formation of a temporary connection between the given stimulus and any inborn activity of the organism, for example: alimentary, defensive, sexual, or orienting.

From the point of view of this basic law, the whole life of a higher animal, and especially of man, consists of continuous formation of new conditioned connections on the basis of unconditioned stimuli that differ in biological quality.

Reasoning thus—and this way now seems to me the only certain way—one must arrive at the conclusion that the cerebral cortex as a whole contains an exceptional diversity of interneuronal synaptic contacts that differ in biological significance. Today we have every reason to assume that the biological difference may pertain not only to whole cortical cells but rather, even, to individual fractions of the synaptic formations on dendrites of the same nerve cell (Anokhin, 1958*a* and *b*; Purpura, 1959).

Indeed, the same cortical cell (for example, a Betz cell), having innervation

relations to a certain muscle, may take part in biologically most diverse fun tional systems of the organism. It may pull the trigger of a gun, write a lo letter, or turn on a motor. From the physiological point of view it is perfect natural to consider this cortical cell, as Sir Charles Sherrington put it, a "chequ payable to the bearer," while the most diverse "bearers" make their deman on it through their own synaptic contacts on its dendrites (Anokhin, 1958*a* and

This natural neurophysiological consideration puts us in a quandary if accept the concept that the generalized desynchronization of cortical elect activity observed by the electroencephalographic method is an indication *nonspecific activation.*

Questions immediately arise that we cannot as yet answer. For examp how does this "activation," diffuse and generalized throughout the cort facilitate the propagation of excitation along the selective synaptic conta that functionally fragment a cortical cell and ensure, in the end, the emergen of a conditioned reaction having a given biological quality, for example, a fense reaction?

If we accept the thesis that the activating effect of the reticular formati on the cerebral cortex is nonspecific, then, considering the incontestable fa that this effect is generalized throughout the cortex, we must arrive at a co clusion that absolutely contradicts all of the vast experience accumulated studies of conditioned reflexes, both in Pavlov's homeland and throughout t world.

As a matter of fact, if we proceed from this generally accepted point of vie we must assume that when a generalized activated state sets in in the cerebr cortex, with desynchronization of electrical activity as the external sign of t state, activation encompasses all the cortical elements regardless of the bi logical activity of the organism with which they were associated in the pa In other words, we must assume that when an animal finds itself in troul and manifests various defensive reactions—and we know on the basis of t experiments performed in our laboratory that this is accompanied by a m powerful activation of cortical activity—at this moment all cortical elemen and all connections formed in the past on another biological basis (for examp the alimentary or sexual basis, or positive emotional states) must also be excit To assume this is to deprive the cortex of its most characteristic ability: t ability to form selective associations, the ability to discriminate.

It is clear that this course of reasoning brings us to physiological nonsen If this really could be so, we should have continuous chaos in cortical activi instead of the finest coordination and always biologically adequate reactio of the animal to the various agents in its external environment.

Reasoning thus we should be faced inevitably with the question: how th can the generalized and apparently diffuse activation of the cerebral cortex combined with the finest selective interactions between the cortical elemen down to and including individual synaptic contacts?

One might think that although the activation of the cerebral cortex outwar appeared diffusely generalized, this generalization nevertheless somehow fac tated the connections and contacts in the cerebral cortex with very prec selectivity for individual synaptic organizations.

Thus a suspicion inevitably arose that despite the uniformity and apparent sameness of the "ascending activations," these were in each individual case physiologically singular, and differed from each other by selectively involving a particular set of synaptic endings and no others.

The experimental verification of these considerations proceeded in our laboratory in two directions:

(1) We made a comparative evaluation of the activating effect on the cerebral cortex in two biologically opposed states: defensive and alimentary. By comparing two biologically antipodal reactions in this manner, we could give the idea of the uniform electric index greater biological and physiological definiteness. In such comparative experiments, conducted by us for the first time, the different biological specificity of the animal's reactions and states served as the differentiating factor that enabled us to determine the physiological significance of the various features of the slow electric activity of the cerebral cortex. In this study we recorded simultaneously from all levels of the brain (cortex, thalamus, specific and nonspecific brain stem reticular formation, hypothalamus), and thus were able to evaluate comparatively the involvement of subcortical and cortical structures at the moment of application of the different conditioned stimuli.

(2) By means of fine electrophysiological methods (stereotaxic and microelectrode evoked-potential technique), we studied the pathways of the ascending influences on the cortical elements under different pharmacological influences and at different stages of ontogenetic development.

Experiments mentioned in the literature already warranted the assumption that there are various qualitatively different structures in the subcortical apparatus, right in the stem reticular formation. In addition to the considerable morphological differentiation, we also have direct and physiological indications. For example, under the effect of nembutal, when the animal or man is in a state of deep sleep, pain stimuli produce no changes in the slow cortical electric activity. On the other hand, in similarly deep sleep but under the effect of urethane, the same pain stimulus leads to a sharp desynchronization of cortical electric activity (Agafonov, 1956).

At the same time the primary superficial cortical potential evoked by a single stimulus of the sciatic nerve can readily be recorded under the effect both of nembutal and urethane; the only difference is that in the latter case its negative component is depressed (Ata-Muradova, 1960*a* and *b*; Lu Juan-hui, 1960).

If we add to this the fact that chlorpromazine prevents desynchronization of cortical electric activity in response to pain stimulation—while the animal remains awake—it will be clear that physiologically and neurochemically the subcortical structures have extremely diverse properties (Rothballer, 1957; Bradley, 1958; Shumilina, 1958; Havlíček, 1958).

All these facts, however, did not as yet warrant a conclusion that this functional diversity of the subcortical structures determined a similarly diverse and selective effect of these structures on the cortical nervous elements.

Direct experiments with conditioned reflexes of different biological specificity were necessary in order to reveal these peculiarities of the ascending influences on cortical activity.

The methods of the first series of experiments consisted of the following: in rabbits with electrodes chronically implanted in different regions of the cortex and subcortex, various conditioned reflexes were elaborated on a basis of unconditioned defensive and alimentary reinforcement. In individual cases the artificial defensive conditioned reflexes were combined with natural conditioned reflexes, that is, with alimentary behavior reactions.

The conditioned reflexes, behavior reactions, and electrical indices from the different regions of the brain were simultaneously taken into account and correlated with a number of autonomic components of reactions, chiefly the respiration and cardiac function.

The experiments of these series have shown that during the performance of the first experiment in an isolated chamber the general reaction of the experimental animal, as a rule, consisted of a pronounced orienting-investigatory reaction, attended by a generalized desynchronization of the electric activity of the cerebral cortex or the appearance of a specific regular rhythm of 4 to 7/sec (see below).

In cases of strong pain stimulation this activation sometimes proves so marked that the entire electroencephalogram becomes a high-frequency one at times forming almost a straight line.

However, if a series of experiments are performed on the same animal in the same chamber, involving no menacing procedures and applying no pain stimuli but, on the contrary, giving the animal some palatable food, this high activation of the cortical elements disappears and the usual slow, high-amplitude activity characteristic of the tranquil state appears.

It should be noted that this "tranquil" electric activity is uncommonly labile and is immediately transformed into a generalized activation as soon as even an insignificant sudden change in the external environment occurs.

This fact once more emphasizes that we must constantly bear in mind that in our experimental situation the animals always have a latent defensive dominance, or, as Pavlov put it, a "biological alertness" (Pavlov, 1938). Besides this fact also may be important for the method since the experimenter may not always notice some insignificant change in the situation that may, however radically alter the character of cortical electric activity. Kohey I, Haracco I described a considerable specific reaction of the rabbit to man. Our experiments have confirmed this observation.

After several months of feeding the animal only palatable food in the given experimental situation, the pronounced generalized activation of the cerebral cortex occurs much less frequently.

However, as experiments have shown, it is sufficient to use electric current only once as an unconditioned reinforcement to cause radical changes in the entire picture of the electric activity of the cerebral cortex. The latter becomes as early as the first day, largely desynchronized, and the animal's behavior is clearly defensive. Records of the autonomic components (respiration and cardiac function) show a complete change in general reactivity, namely, the conditioned stimulation reinforced by electric current accelerates respiration, sometimes completely arresting it in inspiration. The pulse is also considerably accelerated.

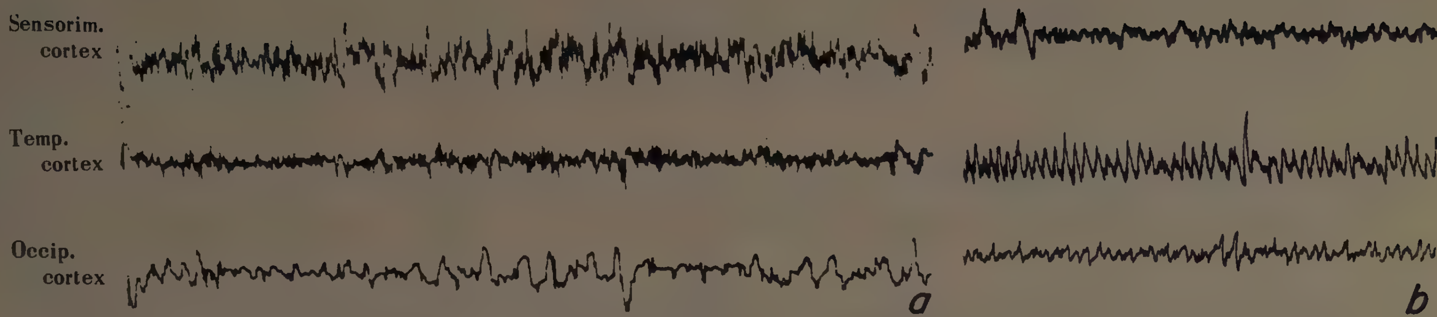

FIGURE 1. (*a*) Continuous desynchronization of the electrical activity of the cerebral cortex, and (*b*) appearance of a regular rhythm ("stress-rhythm") of 4 to 7/sec., corresponding to the defensive reaction and the painful state. Key: SC = sensorimotor; TC = temporal cortex; OC = occipital cortex.

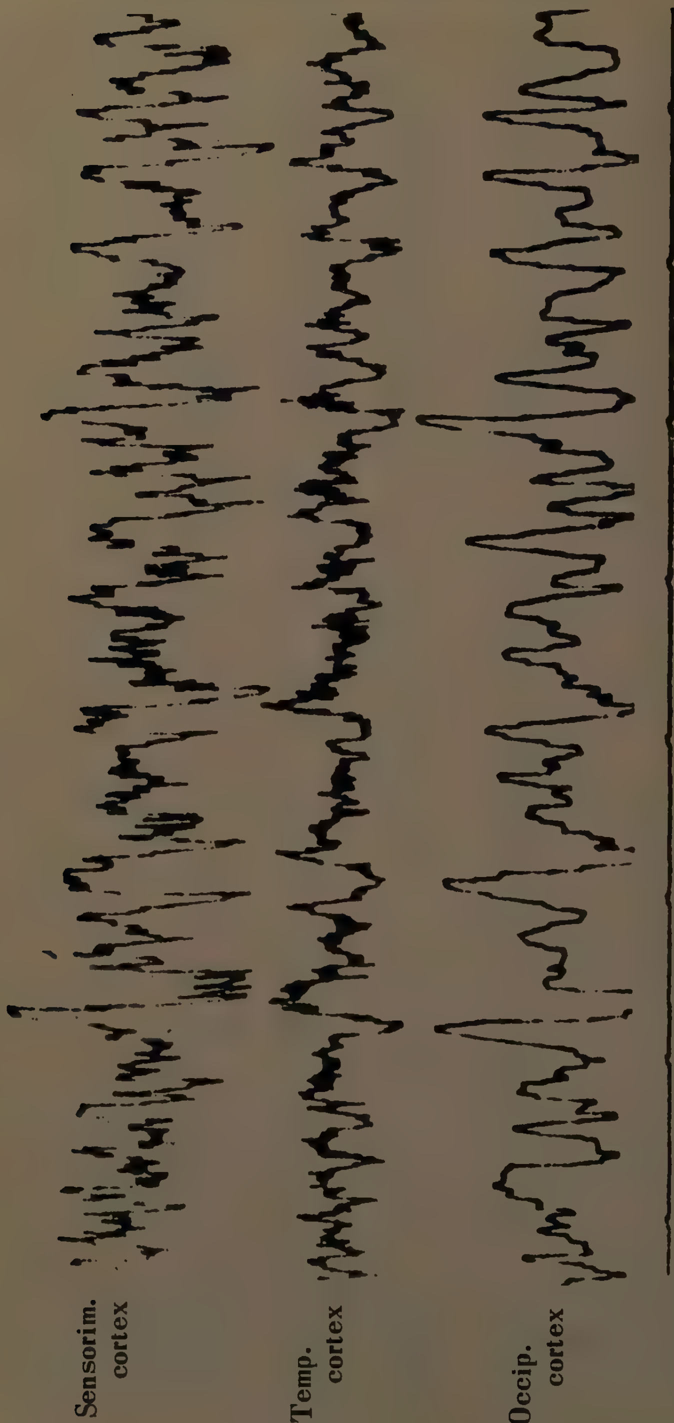

FIGURE 2. Usual slow electrical activity of the cerebral cortex, characteristic of the resting state of the animal. Key: SC = sensorimeter; TC = temporal cortex; OC = occipital cortex.

It should be emphasized that during this period the animals absolutely refuse to take the palatable food they so vigorously devoured during the initial period. In some cases, when the lips of the rabbit were touched with a carrot or beet, the rabbit started, turned away from the food and sometimes jerked away the paw that was being reinforced with electric current. This latter fact is the

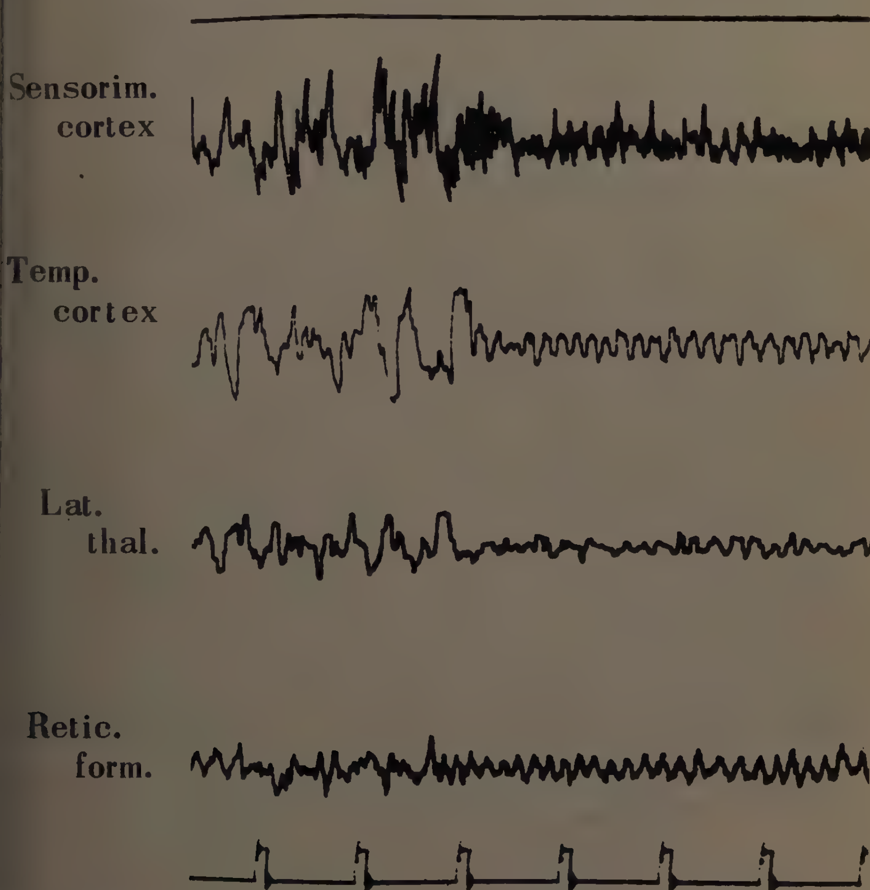

FIGURE 3. Sudden change of the resting electrical activity of the cerebral cortex into a characteristic stress-rhythm (4 to 7/sec.) in response to a slight noise in the experimental chamber.

very best proof that under the described experimental conditions the animal is always in a tense defensive state, which is also accompanied by a generalized and exceptionally marked desynchronization of the electrical activity of the cerebral cortex.

These observations, showing the antagonistic character of the biologically positive reaction (alimentary) and biologically negative reaction (defensive), were made in our laboratory as far back as 1932 from an analysis of the respiratory component of conditioned reflexes of different biological significance.

It has been shown in comparative studies that extinction of the alimentary and defensive conditioned reflexes leads to entirely contrary results if they are evaluated on the basis of autonomic components of behavior.

A sudden removal of the reinforcement of the usual conditioned defensive stimulus leads to elimination of the tenseness in the respiratory movements and ends in their total normalization. On the other hand, a similar sudden removal of the reinforcement of the conditioned alimentary stimulus leads to the appearance of an extraordinarily tense respiratory component, which remains tense for a rather long time (FIGURE 5). It is interesting to note that the character of the respiratory component in this latter case resembles the respiratory curve

FIGURE 4. Rabbit during an experiment with defensive conditioned reflexes. Total refusal of food accompanied generalized desynchronization of the electrical activity of the cerebral cortex.

obtained when the *reinforced* defensive conditioned stimulus is used, a fact that emphasizes still more the antagonistic and qualitatively different character of these two activities.

Summing up this series of observations and considerations, we can draw the following conclusions:

(1) The alimentary and defensive activities of the organism are activities of opposite biological qualities. This fact makes it possible, under certain experimental conditions, to create antagonistic relations between them.

(2) Both activities are capable of evoking a generalized desynchronization of cortical electrical activity, with the sole difference that in experiments with defensive conditioned reflexes this desynchronization dominates and manifest itself even in the intervals between the applications of the conditioned stimuli

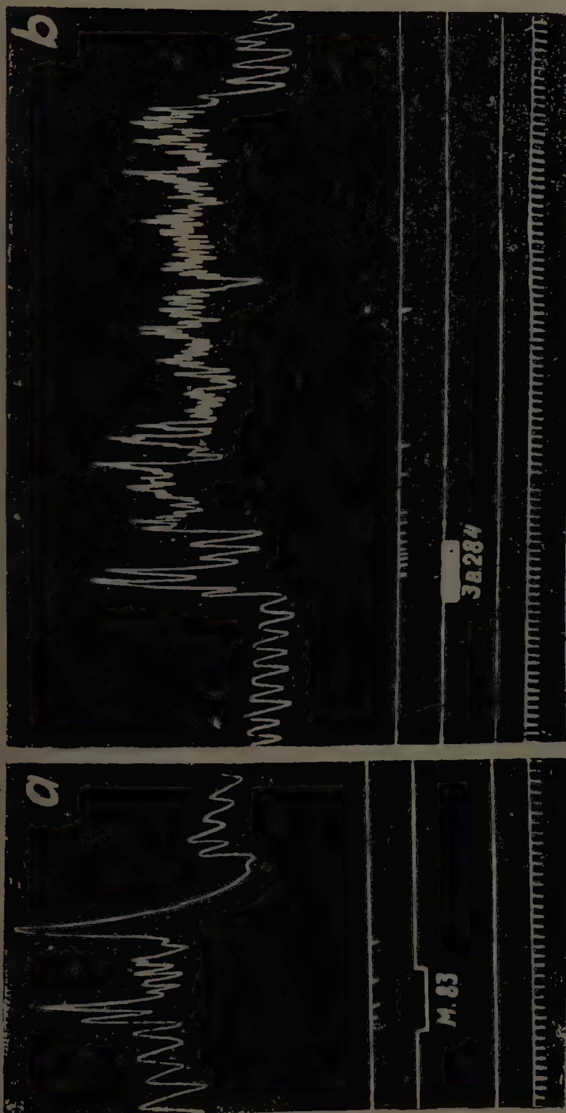

FIGURE 5. Qualitative distinctness of the respiratory component of the conditioned reaction upon nonreinforcement of the defensive and food conditioned reflexes. (*a*) Reaction of the respiratory component to nonreinforcement with electric shock; metronome, 83rd application. (*b*) Reaction of the respiratory component to nonreinforcement with food; bell, 284th application. In the latter case, a sharp activity of respiratory movements is evident.

(3) Considering the different biological properties of the cortical connections developed with the alimentary and defensive conditioned reflexes, we must recognize that in these two cases desynchronization is of different physiological significance, that is, *it must belong to cortical representations of different functional systems.*

On the basis of these general conclusions we made an attempt, first, to separate these two reactions by means of well-known pharmacological agents, primarily chlorpromazine (the Soviet preparation is known as aminazine).

In doing this we proceeded from the following considerations. It is well known that the defensive reaction to pain stimulation is one of the forms of the "stress" type reactions. This reaction takes place, as a rule, with a mobilization of the organism's sympathoadrenal system and reveals itself in extensive muscular efforts (Cannon, 1928). Clinical observations of patients obsessed by pathological fears and melancholy also show that adrenalin and, especially, noradrenalin accumulate noticeably in the blood of these patients.

The investigations of Martha Vogt, who found a large amount of adrenalin-like substances in the posterior hypothalamus and the brain stem reticular formation, support the assumption that the mobilization of the sympathoadrenal system during "stress reactions" takes place to a large extent with the participation of these subcortical structures (Vogt, 1954).

On the other hand, many authors have shown that chlorpromazine acts definitely adrenolytically and deactivatingly, both in the region of the peripheral sympathetic structures (Dell and Bonvallet, 1954; I. P. Anokhina, 1956) and in the region of the central structures (Hiebel *et al.*, 1954; Longo *et al.*, 1954; V. G. Agafonov, 1956; and others).

The localization of this drug's action was shown with particular clarity in the experiments of Bradley and Hans. These authors have demonstrated that chlorpromazine completely deactivates cortical electric activity in Bremer's "encephale isolé" and is ineffective in the "cerveau isolé" (Bremer, 1938).

Collating all these facts, we decided to employ chlorpromazine in the experimental situation described above, that is, when both defensive and alimentary conditioned reflexes were elaborated in our animals.

Aminazine was administered by means of a special apparatus for *distant* injections of different substances into the rabbit's ear. This technique enabled us to administer, when necessary, any dose of aminazine from a considerable distance and entirely unnoticed by the experimental animal.

Experience has shown that administration of chlorpromazine against the background of a dominating defensive reaction, which creates a continuous desynchronization of the cortical electric activity, produces a radical change in behavior as well as in the electroencephalographic indices. A few minutes after administration of optimum doses (about 1 mg./kg.) to the animal, the latter came out of the posture of fear that it assumed in expectation of the pain stimulation. The rabbit moved about very freely, searched for food, examined its feeding trough and greedily devoured the food from which it formerly sprang away. A distinct searching reaction made its appearance.

These changes in behavior are paralleled by a complete transformation in the electrical activity of the cerebral cortex. Within one or two minutes after

the injection of chlorpromazine the marked defensive desynchronization of the EEG gradually gives way to a high-amplitude slow electric activity characteristic of the state of rest.

Particularly interesting is the fact that despite the pronounced alimentary activity, the application of a conditioned defensive stimulus against this background no longer evokes the usual regular rhythms and sharp desynchronization in cortical electric activity, the electric activity remaining as it was at the time the conditioned defensive stimulus was applied.

In its behavior the animal also remains indifferent to the conditioned defensive stimulus, although a show of food or application of a conditioned alimen-

FIGURE 6. The same rabbit as in FIGURE 4 following an injection of chlorpromazine, resulting in resting slow cortical rhythm and marked food excitability. Took food eagerly.

tary stimulus evokes a clear activation of the electric activity of the cortex and a vigorous devouring of the food.

Thus this series of experiments has convinced us that by means of such a substance as chlorpromazine in optimum doses (1 mg./kg.) *we can produce a functional dissociation between two activities of the organism having different biological significance.*

This dissociation can be clearly established from the behavioral, autonomic, and electroencephalographic signs.

On the basis of these data we can express the following propositions from the neurophysiological point of view:

(1) By means of certain pharmacological agents it is possible to block one biologically integral reaction and state of the animal and to free from the inhibiting effect of this first reaction other integral reactions of an opposite biological quality.

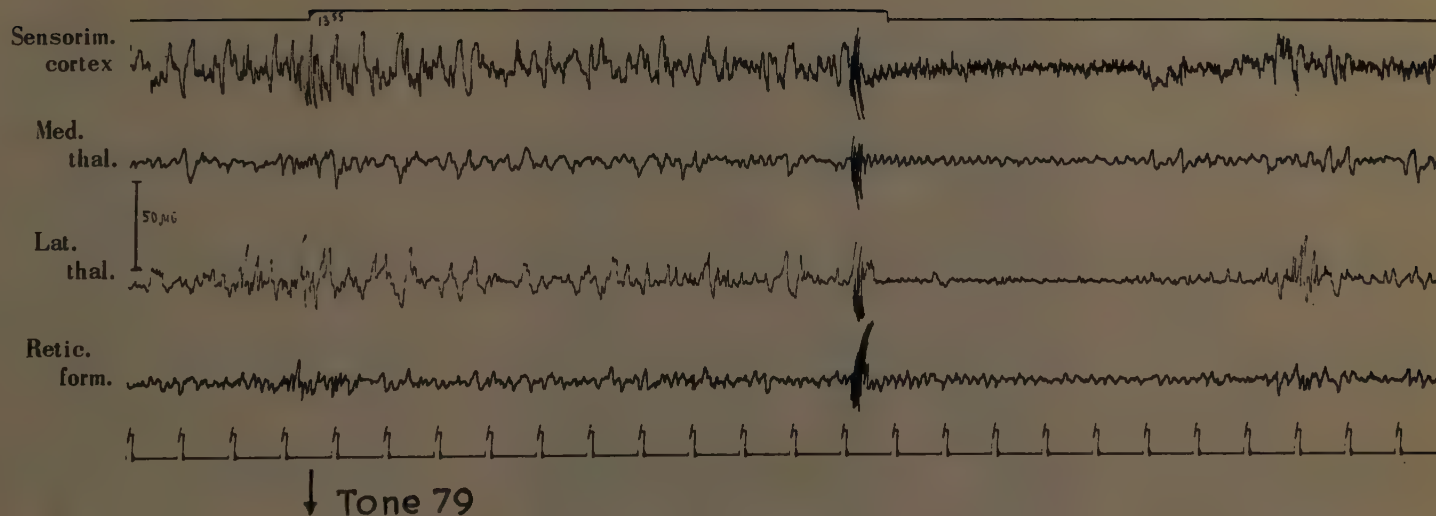

FIGURE 7. Application of a conditioned defensive stimulus following the injection of chlorpromazine. Total absence of cortical desynchronization characteristic of defensive stimuli is evident. Both the desynchronization and the stress rhythm appear for a short period of time when the unconditioned stimulus is applied.

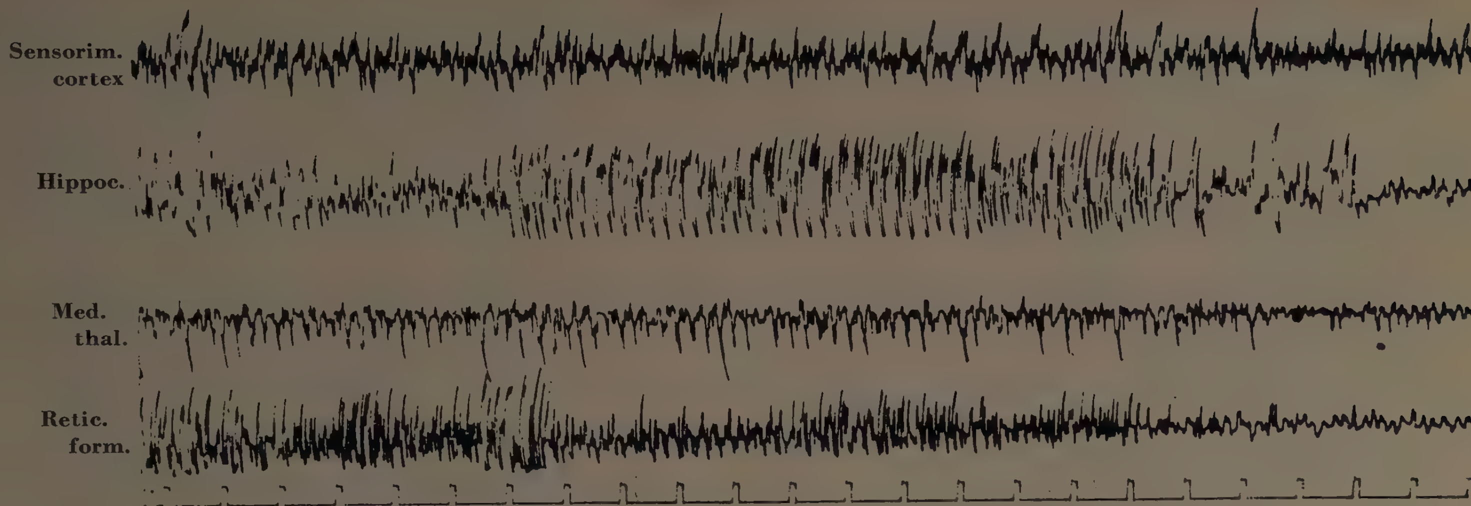

FIGURE 8. The appearance of electrical activity characteristic of the alimentary state during eating.

(2) Since under the influence of an injection of chlorpromazine *all signs* of the conditioned defensive reactions of the animal are eliminated, it may be assumed that chlorpromazine blocks the chemically most decisive and specific part of this widely ramified functional system of the integral organism.

It is difficult to assume that the direct effect of chlorpromazine spreads to all the numerous components of this system. The most reasonable assumption would be that this chemical differentiation of the two biologically different reactions depends on the blocking effect of chlorpromazine on the adrenergic

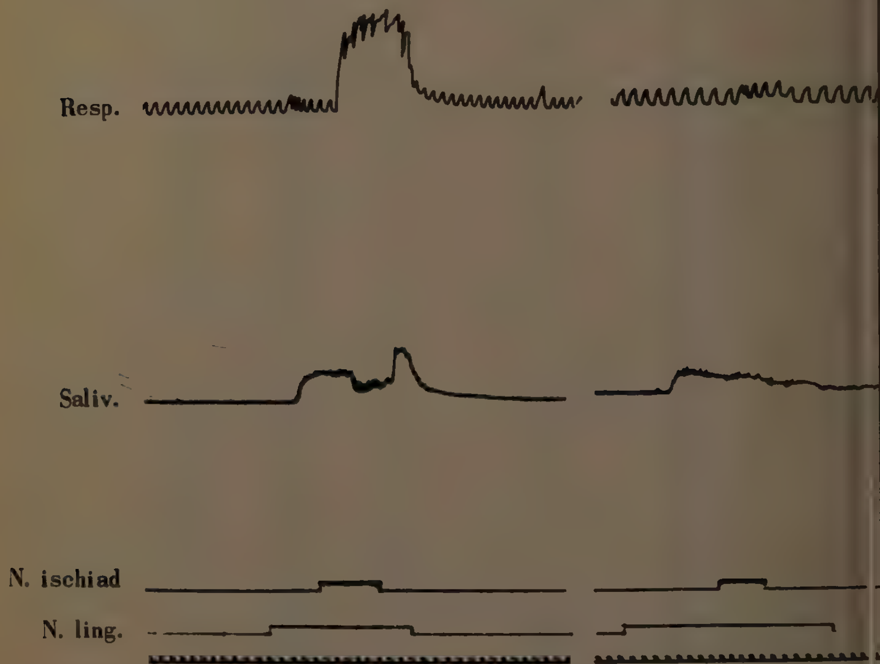

FIGURE 9. Comparative changes in the respiratory component of the pain reaction and in salivary secretion following injection of chlorpromazine in a decerebrate cat. It is evident that following the injection (right side of figure) the respiratory reaction to the pain stimulus is completely blocked.

substrate of the hypothalamus and the brain stem reticular formation (Vogt, 1954; Bonvallet *et al.*, 1954; Agafonov, 1956; Rothballer, 1957; and others).

Experiments conducted in our laboratory on the effect of chlorpromazine on the decerebrate cat are a direct proof that this substance acts precisely on the stem. An injection of chlorpromazine completely eliminates the rise in blood pressure and other autonomic signs of the pain reaction in response to electric stimulation of the sciatic nerve. At the same time such an injection does not eliminate the secretory effect produced in the same experiment by weak stimulation of the chordae tympani (V. A. Polyantsev, 1959).

(3) The conclusions mentioned in paragraphs (1) and (2) collated with an analysis of the cortical electric activity, bring us to a very important assumption that will serve as the point of departure for the further elaboration of our con-

ception of the role played by the subcortical structures in the formation of conditioned reflexes of different biological specificity: the different biological quality of reactions based on different subcortical structures (primarily the hypothalamus and the reticular formation), manifests itself in a similarly fine selective combination of individual nervous connections at the level of the cerebral cortex. This makes possible the separate and specific activation of cortical associations connected by past experience with biologically different activities of the organism.

It may be assumed that all forms of desynchronization of slow cortical activity that arise during the orienting-investigatory, defensive, and alimentary reactions—although outwardly remaining to some extent similar—are actually physiologically entirely specific, ensuring entirely different biological activities.

If this is actually the case, the activation of electrical activity will, at each individual moment, be of a specific nature and we shall have to make very serious amendments to our ideas of the physiological role of the *nonspecific ascending activation* on the part of the brain stem reticular formation.

Our first task, then, was to make a thorough comparative analysis of the forms of electrical activity that attend conditioned reactions of different biological quality.

Comparative Analysis of the Activity of the Cortex and the Different Cortical Structures

All the experimental material described above and the conclusions based on it posed the question before us: are there any features of the electrical activity of subcortical structures that are specific for the defensive and alimentary activities of the animal in its natural environment?

This question is also of localizational importance since, in determining the electric characteristics of the activating subcortical influences on the cerebral cortex, we simultaneously answer the question: Over what anatomical pathways is this influence exercised?

Such questions are quite legitimate.

If the subcortex imparts a biological quality to the behavioral acts of the animal in its natural environment, it would be quite natural to think that this ascending activation, specific and selective in each individual case, should also manifest itself in different forms of electric potentials.

To answer this question we conducted a large series of experiments in which we recorded, through electrodes chronically implanted in different parts of the cortex and subcortical structures, the electric activity during alimentary and defensive conditioned reflexes.

In the first place it was established that during a single electric pain stimulation of the sciatic nerve, or during a more adequate stimulation of a portion of the skin on the rabbit's hind limb, there arose in certain parts of its central nervous system a peculiar rhythm of 5 to 7 cycles per second, which differed from the usual rhythm of rest by its exceptional orderliness and regularity. It was usually somewhat lower in amplitude than the arrhythmic electrical oscillations of rest, but its regularity immediately set it apart as a peculiar electric phenomenon (J. A. Milyagin, 1960; A. Shumilina, 1958; Bantsekina, 1959).

In case of a pain stimulation this rhythm has a very definite and quite stand-

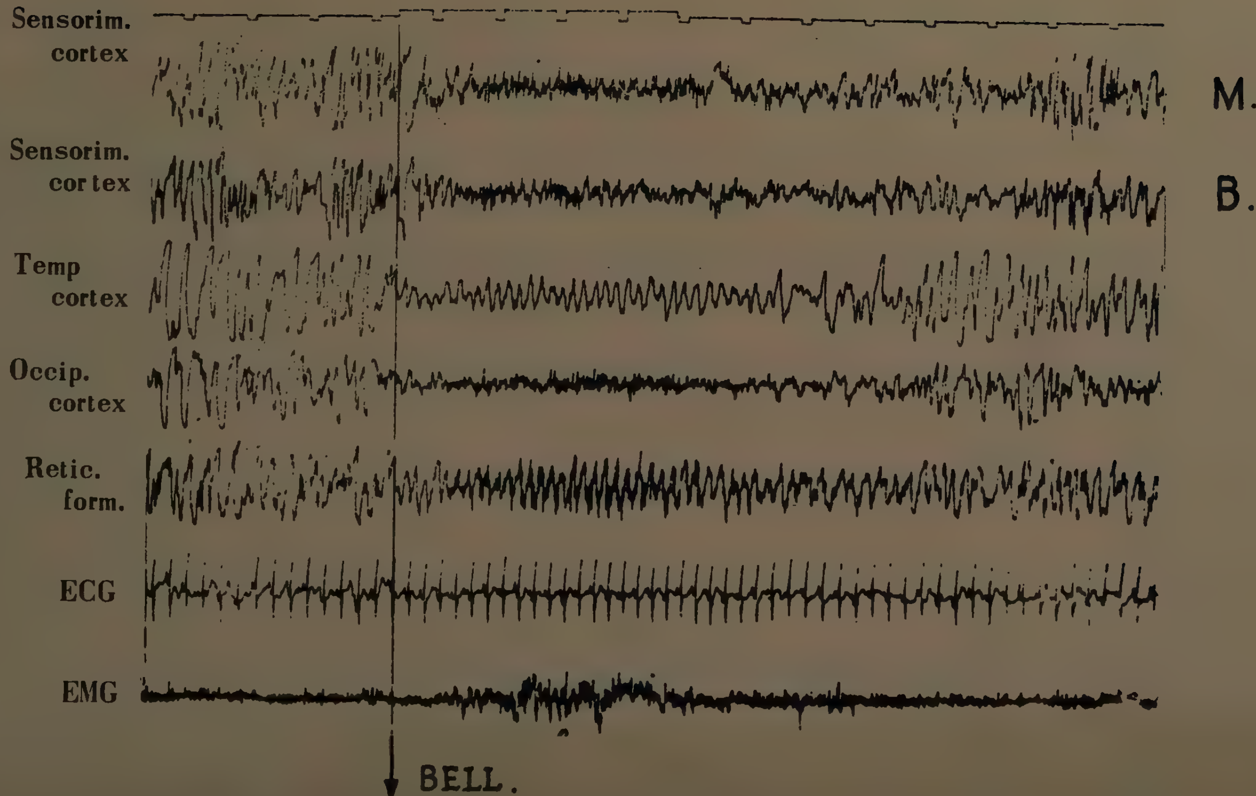

FIGURE 10. Example of a regular rhythm appearing with a defense state in the cerebral cortex (temporal lobe) and in the reticular formation. Desynchronization occurs in the sensorimotor area of the cerebral cortex. At the moment of stress when the bell rings activation of

ard distribution through the different parts of the central nervous system. As a rule, it appears in the rostral part of the reticular formation, the hippocampus, the medial thalamus, and a number of cortical regions: parietal, temporal, and

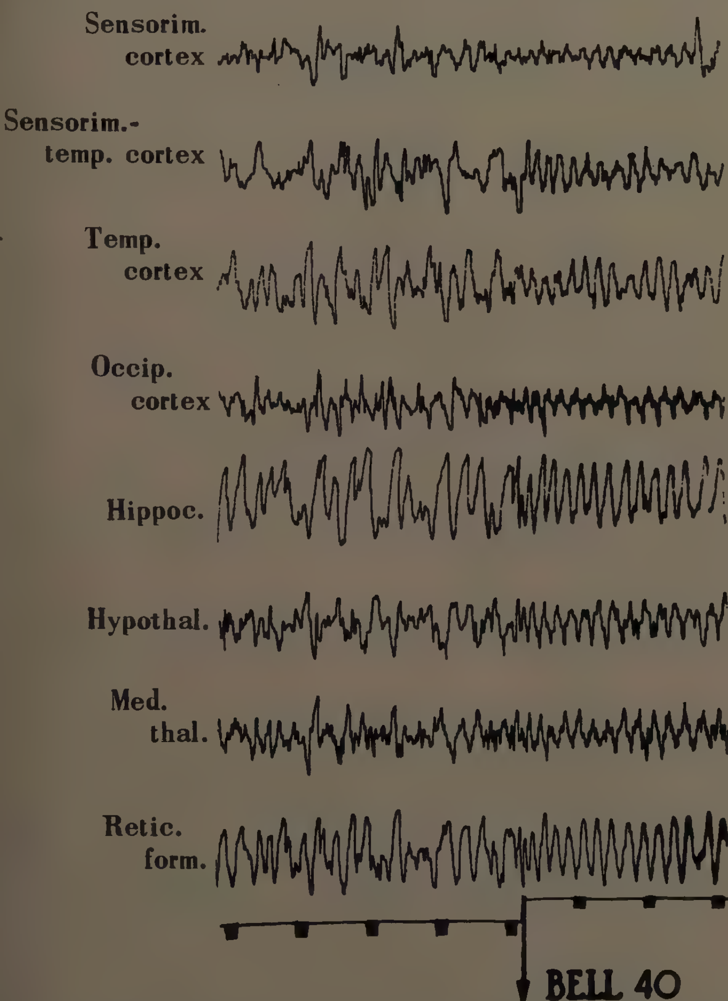

Figure 11. Regular stress rhythms (4 to 7/sec.) in all structures ascending along a vertical line: reticular formation, medial thalamus, hypothalamus, hippocampus, temporal and occipital cortex. As usual, desynchronization of the electrical activity occurs in the sensorimotor area with occasional manifestation of the stress rhythm. Bell is conditioned defense stimulus.

occipital. On the other hand, in response to the same pain stimulation desynchronization appears just as constantly in the sensorimotor area of the cortex.

For the time being we shall set aside the extremely interesting question of why the same subcortical ascending influence produces, in different areas of the cerebral cortex, changes of a different nature in the electrical activity. At

the moment it is important for us to dwell on the identification of this rhythm and its qualitative characteristics as a rhythm attending the algesic state of the organism.

To begin with, the literature contains indications that in certain states of "displeasure" in children, and even in adults, a regular rhythm with a frequency of 5 to 6 cps appears in the cerebral cortex. This rhythm has been given the name of "theta rhythm" (Walter, 1960).

On the basis of thorough studies of this rhythm during our work with defensive conditioned reflexes, we have every reason to think that this rhythm is altogether specific for such states of the nervous system as arise after a pain stimulation or tense expectation of this pain stimulation.

This rhythm arises extraordinarily easily from any accidental stimulation as long as a pain stimulation is effected in the given situation. It is interesting that in all the different situations that ever accompanied the pain stimulation the regular rhythm of 5 to 7 cps always arises in the very same brain structures: the reticular formation, the medial thalamus, and the temporal and occipital cortex. In individual cases the production of any extraneous noise in the experimental chamber caused this rhythm to arise immediately in all these areas of the brain.

We were interested above all in two questions: (1) in what sequence does this rhythm develop in the different brain structures; and (2) what is its neurophysiological significance, that is, to what states of the neural elements does it correspond?

If we reduce the strength of the stimulating electric current, bringing it close to threshold, the regular rhythm begins to appear first of all in the region of the reticular formation, then in the medial thalamus and hippocampus, and only several seconds later, in the temporal cortex where, as is also true of the desynchronization in the sensorimotor cortex, it is at least one half second late. Depending on the variations in a number of conditions, the rates of spread of the regular rhythm may vary in the different brain structures, although the order tends to persist, especially in cases in which the stimulus intensity is low.

The emergence of this rhythm varies most in the different divisions of the hippocampus. In separate experiments this rhythm appears only in the reticular formation and in the medial thalamus, without arising in the cerebral cortex.

By collating all the numerous experiments of this series we can say with a certain amount of assurance that this "stress rhythm" arises primarily in the reticular formation and probably in the hypothalamus, and only then does it appear with various speeds, depending on the strength of the stimulating agent in the other structures, including the cortex. In the light of the very interesting work of the Hungarian authors Lissak and Grastyan (1960) we were particularly interested in a comparative evaluation of the development of this rhythm in the reticular formation and the hippocampus. As I have already mentioned the regular rhythm is particularly variable precisely in the region of the hippocampus and it is, therefore, quite difficult to establish the sequence in which this rhythm arises here compared with the reticular formation. However, in the overwhelming majority of cases this rhythm arises first in the area of the reticular formation and only later, within a fraction of a second, in the hippocampus. It is quite probable, though, that the processes of excitation that

read to the emergence of this rhythm may be in a threshold state, and this rhythm may therefore not always be uniformly recorded in the different areas of the hippocampus. Similarly, the initial state of the structure being studied is undoubtedly also important.

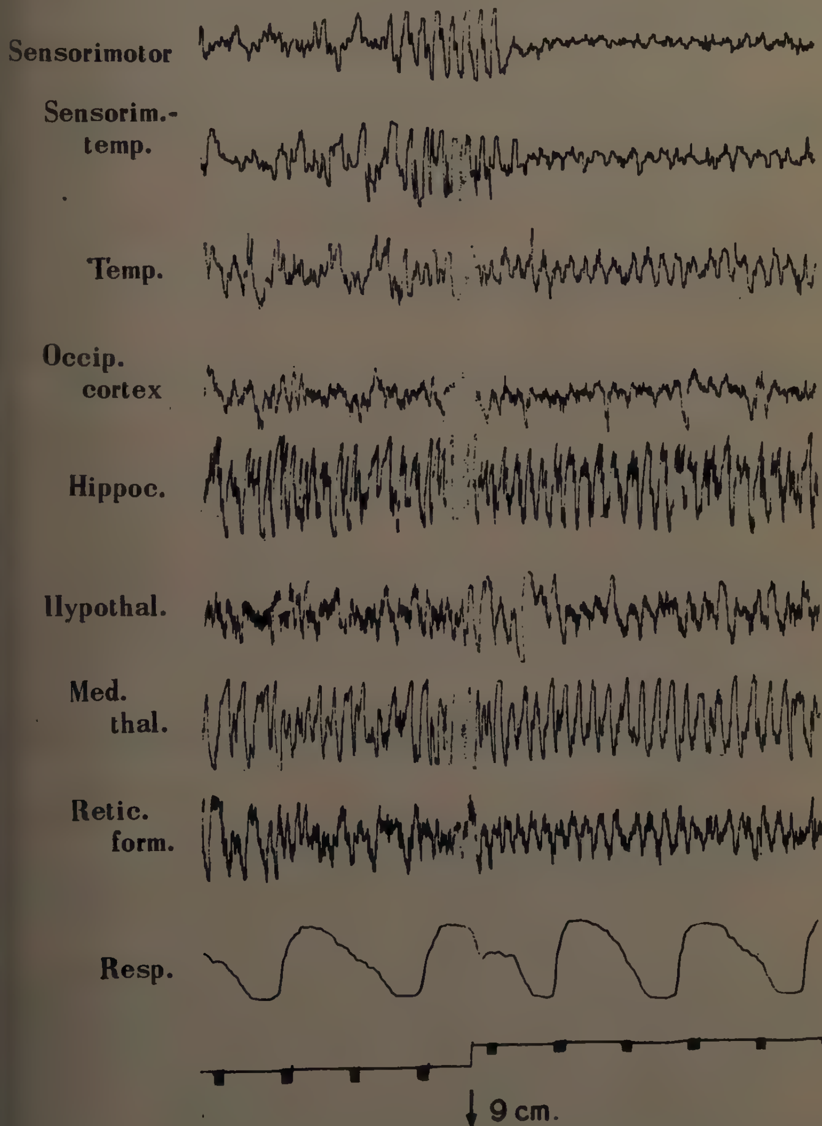

FIGURE 12. When the intensity of the stimulus is decreased, the regular rhythm appears first in the reticular formation; then in the hippocampus, medial thalamus, hypothalamus, and in the temporal area of the cerebral cortex. Such distribution of the stress rhythm underscores the fact that it appears first in the reticular formation. Sensorimotor area is in a state of desynchronization.

We exerted a good deal of effort to check on the extent to which this regular rhythm corresponds, from the point of view of its biological quality, to the state of stress of precisely a pain character or fear of pain stimulation. To elicit this similarity, in individual cases we compared the regular rhythm that arises in response to a conditioned stimulus with the regular rhythm that arises directly after unconditioned, that is, direct pain stimulation. FIGURE 13 shows such a case in which, at the moment a bell was turned on (14th application),

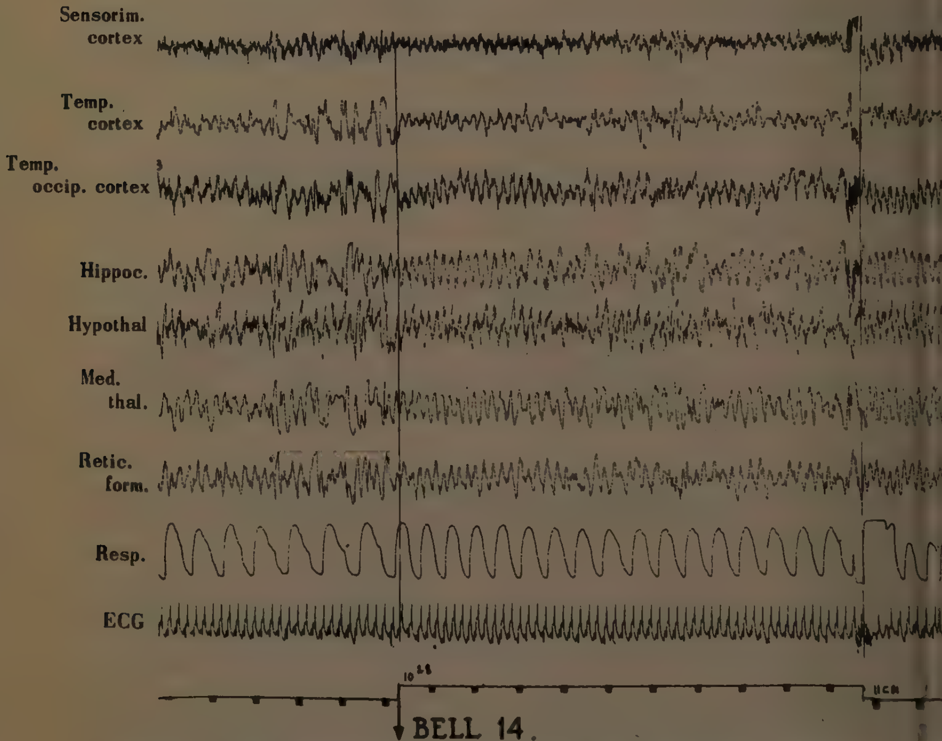

FIGURE 13. Proof that the regular rhythm of 4 to 7/sec. corresponds specifically to the painful state. This rhythm disappears during the conditioned stimulus but reappears in an identical form after the application of the unconditioned pain stimulus.

before it was reinforced by electric current, an absolutely definite rhythm with a frequency of 4 to 6 cps arose in the reticular formation, the medial thalamus, the hippocampus, and the temporal cortex, and desynchronization in the sensorimotor area of the cerebral cortex. The respiratory excursions were accelerated at the same time. However, since this was the very beginning of the elaboration of the conditioned reflex, the general reaction of the defensive character began to disappear in the course of the action of the conditioned stimulus. However, at the moment the relatively weak electric current was turned on, the regular rhythm of electric oscillations reappeared in the structures being studied (after the second vertical line). The electro-

encephalogram shows a striking similarity: the regular rhythm evoked by direct pain stimulation repeats the rhythm produced by conditioned stimulation alone.

All of the foregoing data convinced us that the regular rhythm with a frequency of 5 to 7 cps was an indication of a peculiar state of the central nervous system of the animals (rabbits) that depended precisely on the unconditioned pain stimulus. In other words, this rhythm corresponds to the state of stress

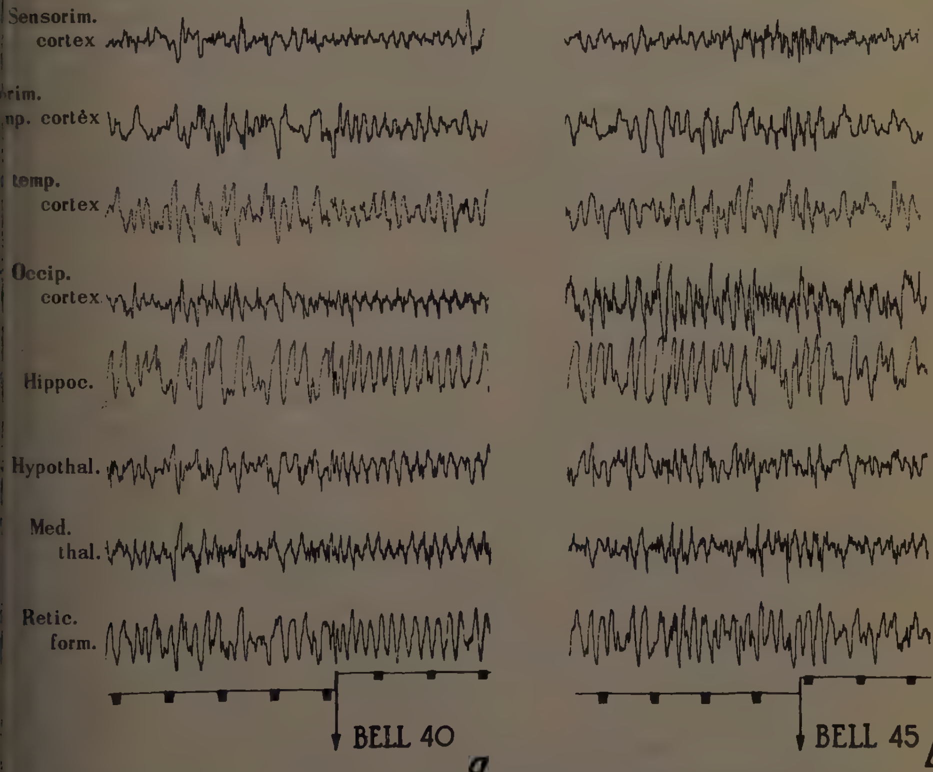

FIGURE 14. Injection of chlorpromazine blocks the appearance of both desynchronization and regular stress rhythm: (*a*) prior to injection; (*b*) after injection.

that arises during biologically negative situations, a fact that gave us reason to name this rhythm the "stress rhythm." It is apparently the expression of the more weakly pronounced biologically negative state that, in a marked and strongly developed form, we observed during the prolonged pain stimulations in the experiments, mentioned above, of Havlíček (1958). It is interesting that chlorpromazine administered to the rabbit in this state also completely blocks the appearance of the stress rhythm.

As FIGURE 14 shows, the conditioned stimulus applied under usual conditions evokes a perfectly distinct stress rhythm that lasts almost as long as the conditioned stimulus. However, the same conditioned stimulus evokes no stress

rhythm after an injection of aminazine, whereas the background rhythm continues unchanged. Thus, by comparing the results of these tests, we can say that the generalized desynchronization of the cortical electric activity that we presented in the first part of our report, and the regular, high-amplitude stress rhythm in the subcortical areas, *are indications of different degrees of biological negative states and reactions of the organism to unfavorable external conditions.*

To this we must add that both forms of electric activity are completely depressed by chlorpromazine and, contrarily, activated by adrenalin, which emphasizes still more the sympathoadrenal basis of the stress rhythm.

A natural question arises: how is this slow, regular rhythm related to the processes that are going on in the nerve cells themselves during these stresses?

If we take into consideration what has been said above about the lack of correspondence between the electroencephalographic picture and the neurophysiological substrate of conditioned reflex activity, we cannot, of course, think that the slow, high-voltage, regular rhythm represents the true interneuronal relations obtaining at the moment the conditioned defensive reaction forms.

To elucidate this very important question we designed a special device that helped us simultaneously to consider the electroencephalographic picture and the state of excitation of the cell elements from the identical point in the central nervous system.

Technically this device consisted of a single electrode, 50 to 100 μ in diameter, located at any point of the nervous structures we were studying, from which we led off and recorded electrical potentials along two directions. In one direction these potentials went through the usual system of amplification, adjusted according to the parameters for leading off slow electrical activity, that is, the usual electroencephalogram. In the other direction, by means of a special filter, only the impulses of a group of cell elements could be recorded. With this device we were in a position to compare, at the very same moment and the very same point of the central nervous system, the state of the slow electrical activity and that of the cell elements.

Modern neurophysiological literature does not contain a sufficiently conclusive evaluation of the slow rhythm from the point of view of the concrete physiological processes that operate in the corresponding neuronal structures. Thus, for example, according to the prevalent opinion, the slow high-amplitude activity corresponds to the inhibitory state of the neural elements (Lissak and Grastyan, 1960; Rusinov, 1951; and others). If we tried to apply this point of view to the aforesaid facts of the stress rhythm, we should find that in the given situation this point of view cannot be applied.

Let us assume that the regular rhythm with a frequency of 5 to 7 cps appears as a result of inhibition of the corresponding neural elements. Immediately, then, we have a physiologically paradoxical correlation that cannot be understood from the usual point of view. How can such widespread inhibition, encompassing almost the whole subcortex and cortex, arise if we apply a conditioned defensive stimulus *that requires the animal to respond with preparatory defensive reactions?*

It is clear that such an assumption is inadmissible from the physiological point of view. Direct investigation involving a comparison of the electrical

activity of the reticular formation at the moment the defensive reaction arises, with the impulses of the cell groups located in the zone of the same electrode lead, has shown that as soon as this regular rhythm becomes accelerated and its amplitude increases somewhat, the corresponding cell elements of the reticular formation begin to produce numerous discharges that are clearly recorded by the previously described method.

As FIGURE 15 shows, the action of the pain stimulus leads to an appearance and noticeable acceleration of the regular rhythm of the reticular formation (upper record), which is accompanied by an emergence of powerful discharges of the cell elements of the same area. This example suffices to dispel the idea that the slow oscillation is an indication of an inhibitory process in the cell elements. On the contrary, the emergence of powerful impulses attests precisely that the pain stimulation that leads to an acceleration of the slow, regular rhythm greatly enhances the activity of the corresponding neural elements.

Thus the rhythm discovered by my colleagues and myself, spreading in the reticulocortical direction, is undoubtedly a rhythm that in some form helps to effect the stress reaction and is connected with an increase in the excitability of enormous cell masses of the brain. In other words, it fully corresponds to our definition of it as the stress rhythm.

It is necessary to place special emphasis on the fact that it is precisely the regularity or orderliness of the slow rhythm that determines activation. Any other form of electrical activity having the same amplitudes of individual slow oscillations, but lacking orderliness and regularity, is not accompanied by nervous impulses.

Careful examination of FIGURE 15*b* shows that the nervous discharges in the cells occur only at the precise moment at which the regular rhythm arises. This rhythm has only to lose its regularity for a fraction of a second and become an *irregular rhythm*, in which the individual slow oscillations retain the same amplitude, for the impulses from the cells to cease. The figure shows very clearly the individual moments when the regular rhythm was interrupted by irregular oscillations. At these moments the discharges of the nerve cells completely ceased.

Summing up this series of experiments, we can say definitely that the biologically negative activity connected with the painful state and general stress of the organism is accompanied by a specific electric rhythm that, with an optimum strength of electrical stimulation, has a frequency of 5 to 7 cps and arises in a definite succession from the subcortical apparatus to the cerebral cortex. This rhythm exactly corresponds to the painful state and probably orients the subcortico-cortical interaction in a definite selective direction.

It was somewhat of a riddle to us that the stress rhythm reaches only definite areas of the cerebral cortex (temporal and occipital). On the other hand, the other areas of the cortex (for example, the sensorimotor area) manifest under the same conditions the usual marked desynchronization of electric activity.

The question is: How can the same force going through the subcortical apparatus produce absolutely different effects in the cerebral cortex? Where are these subcortical streams of excitations transformed either into a slow, orderly rhythm or into desynchronization?

According to the prevalent views, the slow electrical activity of the cortex

FIGURE 15. Comparison of electroencephalogram and mass cellular activity in the same point in the reticular formation. It is evident that the increase in the frequency of the regular rhythm accompanies the increase in cellular activity (*a*). Conversely, the cellular activity ceases when the regularity of the rhythm is disturbed (*b*).

can be formed as a result of fluctuations of the dendritic potentials of the cortical neural elements. This activity is always a certain algebraic sum of the states of the dendritic potentials and the distribution of the afferent impulses that occur at the given moment and with the given stimulus. Two possibilities must be recognized from this point of view: either (1) the initial state of the nerve cells of the sensorimotor area is a special, highly activated state, or (2) at the level of the subcortical apparatus, owing to a transforming activity of some subcortical centers, special high-frequency impulses are sent to the sensorimotor area.

To choose one of these explanatory possibilities, we conducted a series of experiments using various doses of general anesthetics under the same experimental conditions (M. M. Bantsekina, 1960). Experiments showed that with deepening of the anesthetic state the same pain stimulation that had formerly evoked different cortical effects in the sensorimotor and temporal areas of the cortex now began to produce the same effect in the form of a regular slow rhythm, that is, the stress rhythm also appeared in the sensorimotor area.

If we consider the preferential action of anesthetics on subcortical structures, we must recognize that the reticular afferentation to the cerebral cortex, especially the sensorimotor area, has some additional "boosting substations," which here create the effect of desynchronization.

Comparative Analysis of Cortical and Subcortical Electric Activity During Alimentary Unconditioned Stimulation

Parallel with studying the electric activity of the cortex and subcortex in the defensive conditioned reflex, we also studied it in the alimentary conditioned reflex. We did this for the most part in the same animals and through the same electrodes as for the defensive reactions.

The experiments showed that there is a perfectly natural difference between the electrical oscillations with alimentary and electrocutaneous reinforcement.

The experiments conducted in an alimentary situation have shown that the reticular formation, the medial thalamus, and the parietal cerebral cortex manifest electrical activity of a different character without the regular rhythm characteristic of the defensive reaction. It is true that this orderly rhythm appears in individual cases, but this occurs chiefly in the beginning of the action of the conditioned alimentary reinforcement, that is, when the animal responds primarily with a general reaction of alertness. However, one or two seconds after the stimulus is applied, the electroencephalogram changes fundamentally; it ceases to be regular and displays a series of bursts of accelerated and high-amplitude oscillations.

As FIGURE 16 shows, immediately after application of the conditioned food stimulus the reticular formation reacted with the stress rhythm. However this was followed by high-frequency electrical oscillations characteristic of the alimentary state.

These oscillations are not regular; they appear in bursts and in some measure also make themselves evident in other subcortical structures, such as the hippocampus.

It is interesting to note that, when systematically reinforced with food, these high-frequency oscillations also appear from time to time in the form of sepa-

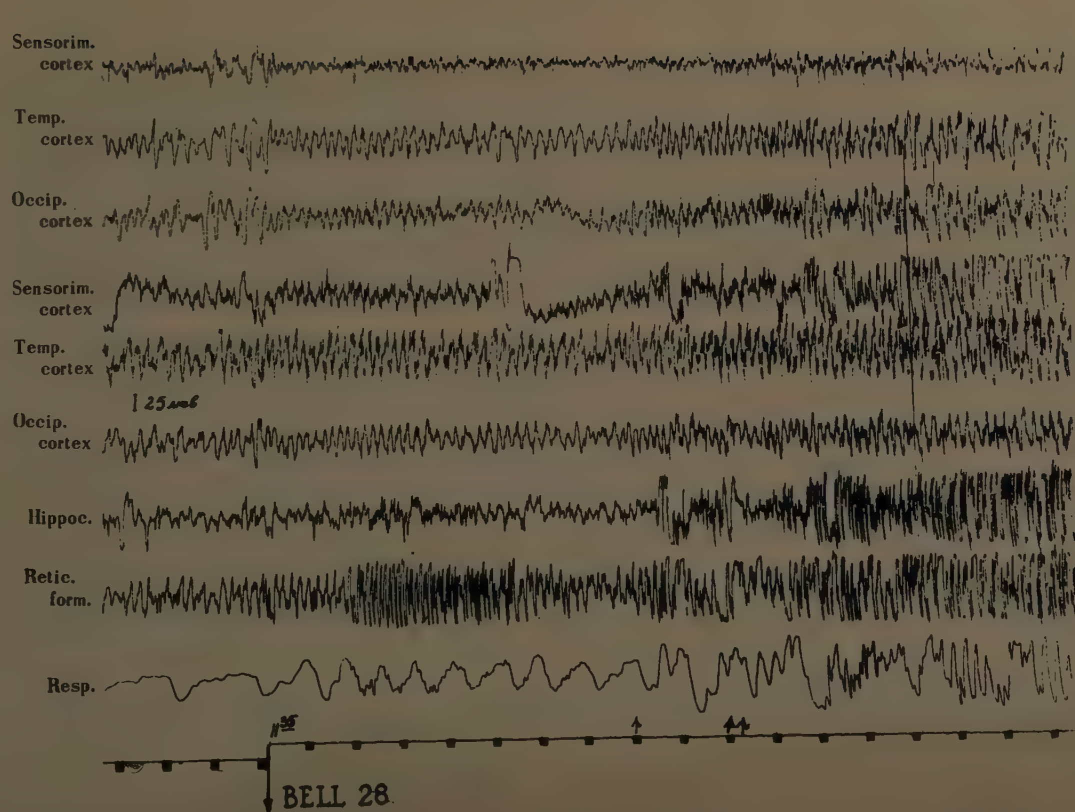

FIGURE 16. Typical change of electrical activity of the reticular formation accompanying changes in the alimentary state. Electrical oscillations of high amplitude and high frequency that never occur in the defensive state are evident.

rate bursts in the intervals between the conditioned stimuli. It should be remembered that under precisely the same conditions, but during work with the defensive conditioned reflexes, the reticular formation and other subcortical structures retained the stress rhythm for a long time.

In FIGURE 17 it may be seen that the flashes of high-frequency oscillations appear regularly against the background of the usual irregular slow rhythm, the so-called "rest rhythm." Although the general picture of electrical activity under these conditions differs sharply from the picture we had when working with defensive conditioned reflexes, it should be noted nevertheless that with sudden intervention of the experimenter the characteristic stress rhythm may come into play even when working only with alimentary stimuli. This fact emphasizes that our experimental animals always retain a latent dominance of the reaction of alertness that, from time to time, comes to the fore under the effect of some external stimuli imperceptible to us.

Summing up this series of experiments we can say that if we exercise caution in the evaluation of the animal's state, the electroencephalographic analysis may yield quite a distinct difference in the electrical activity of the brain during the two biologically different forms of behavior, that is, during defensive and alimentary behavior. This difference manifests itself demonstratively not only at the level of the subcortical apparatus, where it is probably primary, but also in the nature of cortical reactivity.

Thus the specific biological selectivity of the ascending activating effect of the reticular formations on the cerebral cortex is somehow perfectly clearly connected with the different forms of the slow electrical activity, which also spreads in an ascending direction.

Collation of all these facts leads us to the conclusion that the activating influence on the cerebral cortex is always of a functionally specific character; and this is what determines the selective character of the cortical connections that are mobilized adequately to the animal's given behavior act. It is also very probable that the forms of the electrical expression of this activation and the conduction paths to the cerebral cortex differ for the different functional systems.

The foregoing considerations, as well as those already published elsewhere and our own data, warrant the assumption that the influences of the subcortical apparatus on the cerebral cortex must be extraordinarily diverse. Actually each functional system that has any biological peculiarities may influence the cerebral cortex with its own form of activation and its own ways of spreading the afferent impulses. In each individual case the aggregate of these influences is specific.

Forms of Ascending Influences on the Cerebral Cortex

The available data on the influence of afferent stimuli on the cerebral cortex show that they have different pathways of propagation, different types of electrical activity, and different degrees of localization in the cerebral cortex. Thus, for example, the generally known superficial evoked potential of the cerebral cortex has a definite form, is regarded as a specific influence on the cerebral cortex spreading through specific nuclei of the thalamus, and has a rather narrow localization in the corresponding sensory areas of the cortex.

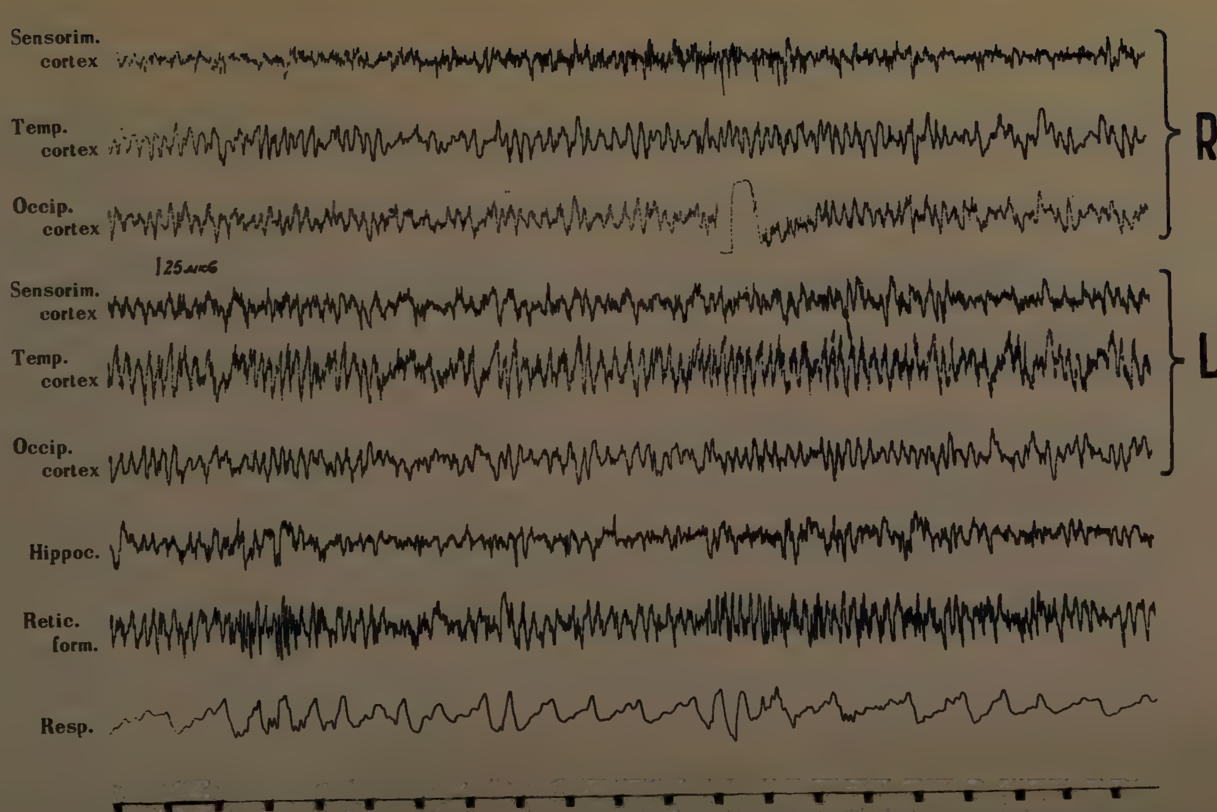

FIGURE 17. Following a prolonged period of experimentation with unconditioned food stimuli, a rhythm characteristic of the alimentary state ... in the intervals between conditioned stimuli

In addition to this so-called primary discharge, Forbes and his collaborators have described also a secondary discharge that comes later than the specific one, has a negative sign, and has wide localization in all areas of the cerebral cortex (Derbyshire *et al.*, 1936; Forbes and Morison, 1939).

These two well-studied phenomena alone should be sufficient to enable us to recognize the extreme diversity of afferent influences on the cellular elements of the cerebral cortex. If, however, we add to them the number of ascending influences on the cortex from, for example, the nonspecific system of the thalamus (Jasper, 1949), the nucleus caudatus, or the hypothalamus, we shall get an idea of how diverse is the afferentation of the cortical elements.

There is no need to dwell on the fact that our knowledge of the entrance of conditioned excitations into the cerebral cortex is directly dependent on how accurately we are oriented in the diversity of the ascending influences on the cerebral cortex.

In recent years our laboratory has carried out a number of studies on a further characterization of subcortical influences on cortical elements. These studies were conducted in the form of parallel recording of the usual electroencephalogram from different fields of the cortex, evoked potentials. Such collation of two different electric phenomena under the same experimental conditions opens up extensive possibilities for characterizing the functional organizations that form the different ascending influences on the cortical cells.

In the first place we studied the special form of the secondary discharge that is connected with stimulation of the sciatic nerve and, as it turned out, is revealed only under urethane narcosis. As is well known, the classical secondary discharge was obtained by Forbes and his collaborators under a nembutal narcosis. If this secondary discharge is eliminated by coagulation of the rostral area of the reticular formation, only the primary response to the stimulation of the sciatic nerve is then recorded in the cerebral cortex, since the lemniscus system is left unaffected by the coagulation.

However, if we transfer the animal to urethane anesthesia after the effect of Nembutal has worn off, a distinct secondary discharge, similar to Forbes's secondary effect but with a greater latent period (FIGURE 18), is gradually revealed.

Since the rostral part of the reticular formation is coagulated, it is clear that this secondary effect does not depend on it, although it is evoked by stimulation of the sciatic nerve. Additional coagulation of the subthalamic area leads to the disappearance also of this "urethane secondary response" (studies of Lu Juan-hui, 1960).

These experiments reveal the remarkable properties of different anesthetics that open up various subcortical "gates" for the spread of afferent excitations to the cerebral cortex. The studies of Mary Brazier, conducted in recent years, have shown that the deepening of anesthesia may suddenly reveal activity that had previously been blocked (Mary A. B. Brazier, 1954).

This fact emphasizes once more that our knowledge of subcortical activating influences on the cerebral cortex is far from perfect. These influences are connected not only with the form of stimulation, but also with the form of the anesthetic we use in the given experiment.

The anesthetic, as the experiments of many of my collaborators (Agafonov,

Polyantsev, Ata-Muradova, Atseyev, Lu Juan-hui, and others) have shown creates in different subcortical structures a peculiar filter through which som afferent activating influences reach the cortex, while others are blocked. Thes relations may be entirely reversed by changing the anesthetic.

Still more interesting facts about the diversity of afferent influences on th cerebral cortex are furnished by ontogenetic studies.

The studies of F. Ata-Muradova (1960), a worker in our laboratory, on new born rabbits have shown that even the classical primary superficial potentia that arises in response to a single stimulation of some receptor surface is not s simple as is generally assumed. By effecting a single stimulation of the sciati

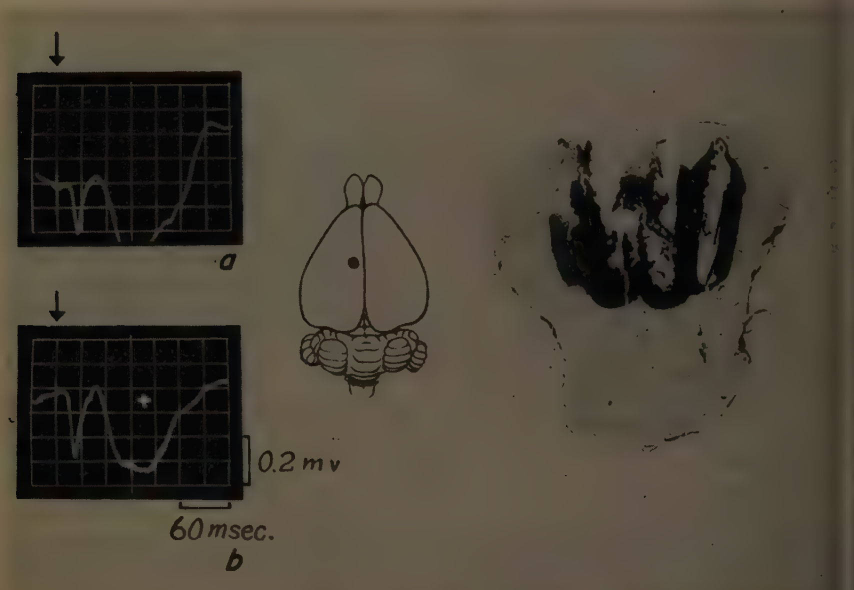

FIGURE 18. Appearance of a secondary discharge with urethane anesthesia followi coagulation of the rostral region of the reticular formation. This proves that in this ca we are not dealing with a secondary Forbes discharge (denoted by a cross). See text.

nerve of newborn rabbits, she showed that during the first days after birt only the *negative* component of the primary potential was recorded, wherea the positive component, which usually precedes the negative componen distinctly manifests itself toward the 11th day.

This order of maturation of the primary potential totally contradicts th generally accepted conception of its nature, based on an assumption of th electrical homogeneity of the two phases of the evoked potential. If we adop this latter conception, we could not possibly obtain only the negative compo nent without the positive component, since the former is a result of the latte A further characteristic that does not agree with the electrical homogeneity the two phases of the primary potential was observed in Ata-Muradova experiments. It turned out that the negative phase of the primary potenti was extraordinarily sensitive to various chemical influences.

Ata-Muradova's experiments have revealed that urethane acts selectively only on the negative component of the evoked potential, completely blocking it, but at the same time does not influence, or influences but very slightly, the positive component of the evoked potential.

These observations, compared with the different rates of maturation of the ascending fibers of the specfic and nonspecific system, warrant the serious assumption that the positive and negative phases of the evoked potential arise as a result of the different pathways along which the afferent impulse enters the cerebral cortex. A comparison of our data with those of Bishop, 1936, 1958; Purpura, 1959; Grundfest, 1958; and others, shows that the negative component of the evoked potential may be ascribed to the rather swift passage of the afferent impulse through the ancient spinothalamic system and the lateral nucleus of the thalamus.

Thus Ata-Muradova's experiments on newborn rabbits extend our ideas of the scope and diversity of the afferent influences of the subcortex on the cortical cell elements. It can hardly be doubted that each of these influences on a cortical cell contributes a certain part of its own specific effect that, in some way, facilitates the complex integrative processes in the cerebral cortex. This once more emphasizes the exceptional multiformity of information about the cortical level of integration of the volley of afferent impulses.

General Remarks and Conclusions

Summarizing these observations, we may say that by their numerous and diverse influences on the cerebral cortex, effected through various pathways, subcortical structures constantly participate in the formation of the conditioned reflex as an integral behavior act.

In the first place it should be pointed out that the subcortical structures determine the decisive direction along which the cell elements of the cerebral cortex selectively unite in functional systems of different biological quality. Here the general idea of the single form of nonspecific ascending activation of the cerebral cortex is entirely inadequate.

The types of ascending influences discussed above are, of course, not the only ones. We may aver that subsequent studies will increasingly extend the nomenclature of the primary and secondary influences on the cerebral cortex available today.

It is important to know that for each nervous act these influences have a peculiar arrangement and always a specific effect on the cortical synaptic organizations.

We point out, for example, that the "secondary discharges" obtained by Forbes and by Lu Juan-hui in our laboratory, although generalized throughout the cortex, obviously cannot be identified with the generalized activation revealed in the desynchronization of cortical electric activity.

To be sure, under conditions of deep anesthesia induced, for example, by Nembutal, the desynchronization in response to pain stimulation is completely eliminated. However, the secondary discharge arising in response to a single stimulation of the sciatic nerve in all the areas of the cortex proves, under these conditions, to be even more pronounced. It is clear that the subcortical apparatus that determines the generalized secondary discharges in the cerebral

cortex and the apparatus that determines the generalized desynchronization also in the cortex, are of different physiological significance.

It should also be remembered that while eliminating the activation of the cerebral cortex from the conditioned pain stimulation, chlorpromazine nevertheless leaves the animal in a waking state. This relationship of phenomena is possible only if the pain activation of the cortex and the activation creating the waking state are effected along separate and independent pathways.

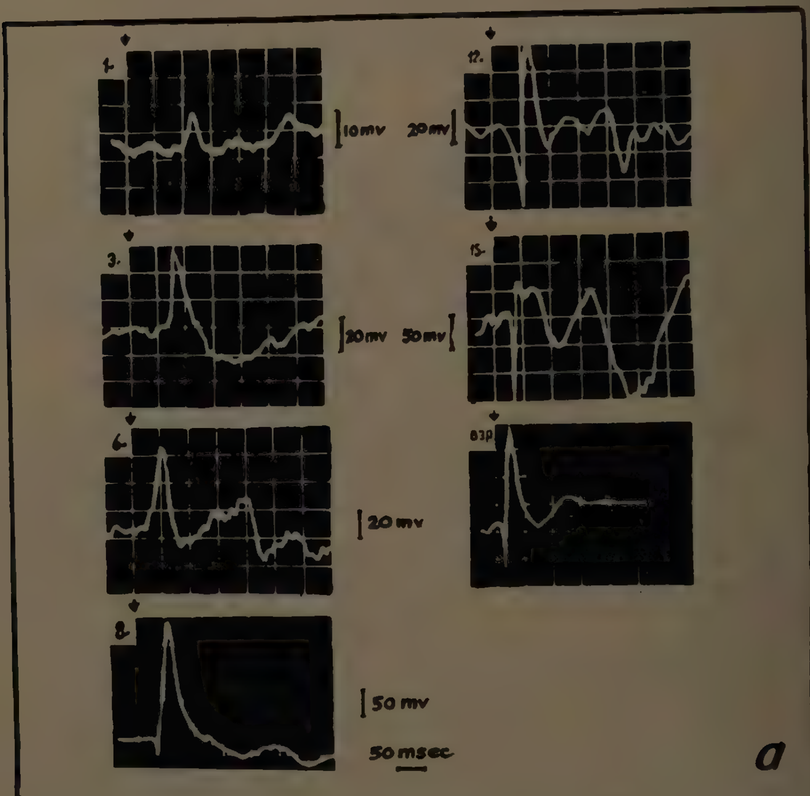

FIGURE 19. In ontogeny the negative component of the primary evoked potential appears first, independently of the positive component. (*a*) Gradual growth of the negative component and appearance of a positive component as a function of age of the newborn. (*b*) Local application of 1 per cent solution of GABA removes the negative component, when it appears alone (fourth day after birth).

This multiple and independent ascending control of the cerebral cortex can be demonstrated in a more distinct form by experiments with direct stimulation of the brain stem reticular formation.

The following comparison of different forms of ascending activation was made in I. P. Anokhina's experiments (1956). First, by application of strychnine paper, synchronized discharges generalized throughout the cortex were obtained, and then a direct electric stimulation of the rostral part of the reticular formation was effected. Experiments have shown that stimulation

of the reticular formation produces a desynchronization of the background slow electric activity typical of it, although paroxysmal epileptiform discharges continue to reach the cerebral cortex. Naturally, this can happen only if the cortical neurons have two separate controls with some measure of physiological independence.

Collating all these data we become still more convinced that the specific

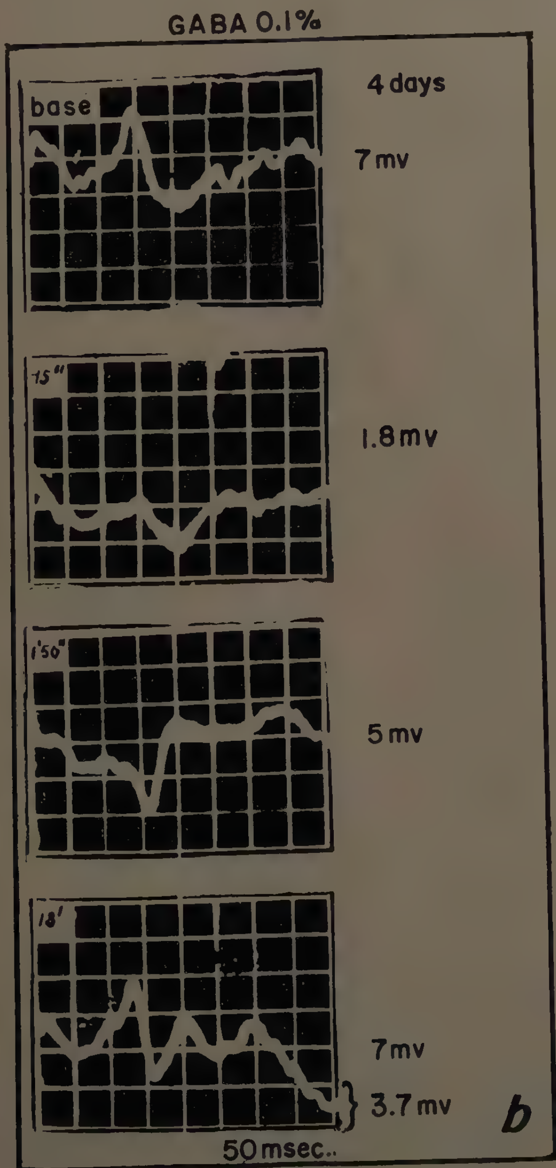

FIGURE 19 (*b*).

ascending control of cortical activity, or, to be exact, the formation of an afferent synthesis of all the diverse ascending excitations, is always the initial stage of any form of cortico-subcortical interaction.

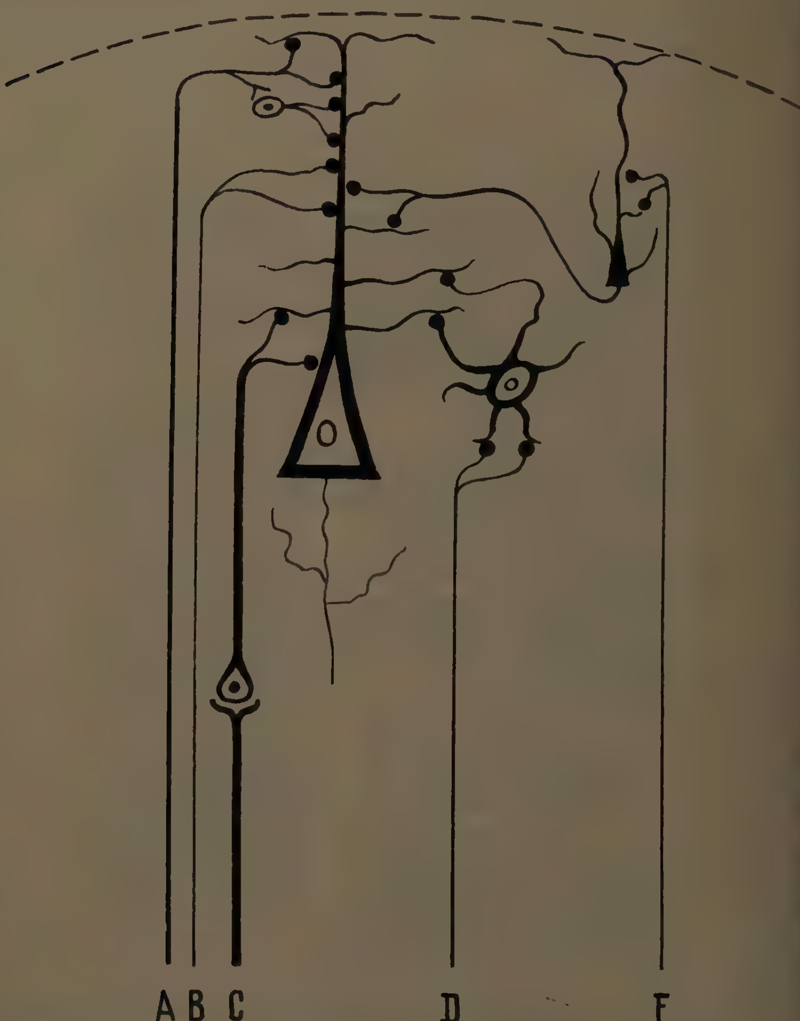

FIGURE 20. A model showing the plurality of ascending action on the same cortic[al] neuron. (*a*) Assumed nonspecific control, when the negative component appears ontogene[t]ically; (*b*) other controls of apical dendrites; (*c*) specific thalamic control; (*d, e*) other vario[us] ascending controls of cortical neurons.

For the physiologist of higher nervous activity it is especially important tha[t] in any conditioned reflex act, beginning with the first application of the con[-]ditioned stimulus and ending with the complete establishment of the temporar[y] connection, the cerebral cortex is simultaneously subjected to numerous affe[r]ent influences along many ascending subcortical pathways.

We see that these pathways are always integrated on the basis of a biologi-ally definite activity and, consequently, the so-called "nonspecific activation" f cortical processes is always a biologically qualitative peculiarity.

Only the imperfection of the electroencephalographic index fostered the mergence of the ideas of a "generalized," "nonspecific," and "diffuse" activat-ng effect of the subcortex on the cerebral cortex.

This important factor in the formation of the conditioned reflex—the path-ays along which the multiform information reaches the cerebral cortex, and he synthesis of this information—is the basis on which the formation of any daptive act begins (Anokhin, 1959).

We have seen that the brain carries out this work in such a manner that, n it, the nonspecific activation (in the sense that it facilitates the action) is lways *selectively* included in the specific, which determines the fineness of oordination and the precision of adaptations.

How do these two forms of activity, seemingly so antagonistic in their hysiological characteristics, combine?

However, a most important question immediately arises: What anatomical tructures underlie these diverse subcortical influences on the cerebral cortex?

Several years ago we expressed the idea that the numerous synaptic con-ections of the cortical neurons, especially those neurons with a ramified den-ritic system, are the most probable site of selective perception of the diverse scending influences, as well as intracortical associative excitations (Anokhin, 958*a* and *b*).

A remarkable recent review by Purpura (1959) of the modern state of this roblem shows that today this path is really the most fruitful.

The foregoing data warrant the assumption that nearly every cortical neuron as on its body and dendrites numerous synaptic contacts from all the numer-us ascending influences.

In this functional sense each cortical neuron is an exceptionally heterogeneous tructure, and it is possible that each homogeneous synaptic organization on he cortical neurons, when excited, is capable of producing by itself one elec-roencephalographic effect or the other: desynchronization or synchronization. f this were really true, we could understand, for example, the facts of separate esynchronization of cortical electric activity in the defensive and alimentary onditioned reflexes (see above).

One more essential point still remains unclear in this great problem, a point o which we shall, however, be unable to give due attention here.

On the basis of what mechanisms, in response to the corresponding condi-ioned signal, does a reaction arise with precisely a given biological quality: hat is, a defensive, not an alimentary, quality, or vice versa?

As I have observed in this paper, the biological quality of the activation of ortical activity and cortical integration, in general, is determined by the haracteristics of hypothalamic and reticular activity.

However, how did this activity come into play?

With this question we approach the problem of corticifugal influences on the ubcortical apparatus.

To be sure, we rejoice at the sight of some friend or person we like, because t first *we recognize* this person by singling him out of hundreds of similar per-

sons, and only then does the emotional apparatus of a definite quality com into play. It follows that any reaction of the brain includes in its initial par at least three decisive stages:

(1) The stage of synthesis of all the afferent influences on the cerebral cortex including all the ascending influences resulting from the subcortical analysis of the initial stimulation from the external world.

(2) The stage of inclusion, in the subcortical complexes, of a definite biologi cal quality adequate to the entire given surroundings.

(3) The stage of selective ascending subcortical influence on vast areas of th cerebral cortex, where the final integration of the nervous processes precedin the formation of the behavioral act as a whole takes place.

The interesting thing is that all three stages, as revealed by experiment an day-to-day practice, develop in the space of fractions of a second. This i the real dynamism in the work of the brain, the understanding of which con stitutes our common aim.

Several years ago I advanced a concept for the understanding of the genera physiological architecture of the conditioned reflex (Anokhin, 1959).

This architecture includes several decisive links, the first and most importan of which is the *afferent synthesis* by which the formation of a particular be havioral act, as well as the control of its effectiveness by means of retur afferentation, is determined.

The present paper has been devoted to a consideration of the precise neuro physiological mechanisms of the afferent synthesis stage.

In recent years we have been acquiring more and more exact data about th vast horizons of this most important mechanism. At one time Pavlov figura tively named the afferent function of the cortex the "creative function (Pavlov, 1938, 1949).

It seems to me that the material offered by us in this report once more ind cates convincingly the proper evaluation of the afferent function of the cerebra cortex and, at the same time, shows the vast horizons that open up befor Pavlov's pupils and followers in characterizing the multiform neurophysiolog cal processes synthesized by evolution in the conditioned reflex.

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THE ROLE OF SUBCORTICAL STRUCTURES IN CONDITIONED REFLEXES

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Anokhin has made two major points of great importance for theories of igher nervous activity. First he has emphasized that in complex, learned ehaviors the cerebral cortex is not acting alone, but is in close association ith subcortical systems. With the rich interchange known to exist between nese systems it is appropriate to seek the mechanism of conditioned reflex ormation and performance in the cortical-subcortical relationships rather han predominantly in the cortex itself. While pointing out this importance f subcortical structures, Anokhin has also clearly demonstrated that they re intricately organized and cannot be regarded simply as an indiscrimi-ate "energizing influence" on the cortex. His experiments repeatedly and onvincingly documented this second point. Together with many other facts ney should convince us that the medial brain stem systems are capable of more recise action than is indicated in their diffuse or "nonspecific" effect upon the EG.

I am certainly in agreement with Anokhin on both of these points. Thus, ather than discuss details of his paper or simply restate his case, I hope it will e more valuable to offer a summary of data, for brevity and convenience taken hiefly from our laboratory, which give general support to his view and are elevant to his consideration of the role of subcortical structures in conditioned eflexes.*

Using a defensive conditioned reflex (CR) in cats, we found during the course f training that EEG arousal reactions to an auditory conditional stimulus (CS) lways attained a high level of consistency before the first respiratory or flexion R appeared.[1] Prima facie this indicates participation of subcortical mecha-isms, although obviously the effect might be initiated from the cortex. Graphs f the per cent occurrence of these EEG arousal reactions had the form of ypical "learning curves" for habituation, conditioning, and extinction. Sur-risingly, however, under the conditions of these experiments "habituation" of he arousal reaction to the CS seemed to take place during the early training, ven though a shock to the leg was being paired with the CS. Another un-xpected finding was that the intensity of the arousal reaction diminished after he CRs became consistent, and with continuation of training a state was eached at which leg flexion CRs could be made with no apparent alteration in he electrical activity of postcruciate, marginal, and middle ectosylvian gyri.

Pursuing this matter independently, Edward Beck and his colleagues at the niversity of Utah[2] have found with sleep-deprived cats that when such flexion Rs are made in the absence of low-voltage fast activity in the neocortex, a hange in activity is still always found in certain subcortical areas. The

* The original work described in this discussion was performed in the laboratories of the niversity of Michigan under Research Grant B-1068 from the National Institute of Neuro-gical Diseases and Blindness, Public Health Service, Bethesda, Md., and by a research grant om Foundations' Fund for Research in Psychiatry, New Haven, Conn.

mesencephalic reticular formation is one of the areas in which such alteration occurs, and is sometimes the first to change its pattern of activity. More often, however, the changes prefacing CR performance occur in the hippocampus and septal areas, and precede those in the mesencephalic reticular formation.

It has been found that defensive CRs can be obtained after destruction of the central core of the mesencephalon, including the reticular formation, or after destruction of the posterior hypothalamus and central thalamus in the stereotaxic planes A-10 to A-12.[8] In one animal however, there was some indication that certain subcortical structures may be indispensable for this type of conditioning. This animal responded well preoperatively but, following destruction of about 100 mm.^{3} of the medial brain stem, including the mammillary bodies, center median, field H_1 of Forel, and the habenulopeduncular tract, the animal made no CRs in 1325 trials in 26 training sessions over 3[illegible] days. EEG patterns were within normal limits after the third week, but likewise showed no evidence of conditioned reactions. This animal, although it failed to give CRs, was no more debilitated postoperatively than others with different lesions, which responded adequately. The negative findings thus appear significant.

Since it is difficult to maintain such animals with large bilateral subcortical lesions and since the poor condition of the animal makes it difficult to interpret negative data, Lester Rutledge and I have devised a somewhat different technique for seeking the "indispensable" subcortical structures. In cats trained to flex a leg to a tone, the hippocampal and anterior commissures and the corpus callosum are cut and a large lesion placed subcortically on one side. Direct electrical stimulation of homotopic points on the cerebral cortex is then used as CS, and CR performance is compared for stimulation of the intact side and that with the subcortical lesion. Lesions that seriously encroach upon the internal capsule make stimulation of the ipsilateral middle ectosylvian gyrus ineffective as CS. However lesions confined to the medial geniculate body or transecting and unilaterally destroying the medial thalamus, hypothalamus, and mammillary body in the stereotaxic planes A-7 to A-10 have not altered the effectiveness of the middle ectosylvian gyrus CS.

Although destruction of the habenulopeduncular tract in the latter cases has thus far not been adequate to permit full comparison with the bilateral lesion described above, one is nevertheless forced to consider the possibility that should there be an "indispensable" brain stem region, it may be activated by diffuse subcortical commissural pathways. Corneliu Giurgea (personal communication) in 1957 on one dog had been able to link a CS electrically applied to one hemisphere to a "US" applied to the motor analyzer of the other hemisphere, even though the entire brain had been completely split from the frontal pole to the anterior border of the mesencephalon. Following section of the corpus callosum, Rutledge and I[9] have also found no difficulty in producing CRs in limbs ipsilateral to the cortically applied CS.

When electrical stimulation of the cerebral cortex is used as a CS, undercutting the stimulated zone at first destroys the effectiveness of the CS, whereas circumsecting most of the stimulated cortex does not.[4,10] Thus a direct projection into subcortical circuits seems to be more important here than intracortical elaboration.

Once a CR is established to one stimulus modality or location of central stimulation, it is usually readily elicited by other stimuli either immediately or with very little training.[9] Sarah Southwick and I (in unpublished observations) have confirmed this tendency for stimulus generalization or transfer of training when stimuli are applied almost any place in the brain stem of the cat. Highly similar results have been obtained by Nielson *et al.*[18] In rare instances[17,18] the central stimulation is ineffective, perhaps because of unrecognized technical difficulties. A situation of great interest also arises when the central CS in highly trained animals remains ineffective for a training period of several days or weeks and then rather suddenly begins to elicit CRs.[5,9] Such cases are uncommon, however, and it seems safe to say that with adequate training. electrical stimulation applied any place within the nervous system can elicit a CR. In other words, there are no "silent" areas in this regard. This conclusion can be drawn from extensive data on widely varying placements on the cat cerebral cortex,[7,9] from about 52 subcortical placements by Nielson *et al.*,[18] and from more than 30 subcortical placements in the unpublished studies of Southwick that ranged from the trapezoid body to the septal nuclei. The same conclusion appears to hold for the monkey (*Macacus irus*), in which stimulation of such varied regions as the occipital lobe, the precentral, postcentral, marginal and supratemporal gyri, the regions around the arcuate and principal sulci, the inferior colliculus, inferior pulvinar, or reticular nucleus of the thalamus is capable of eliciting a lever-pressing CR for shock-avoidance. With sufficient training a single 1.0 msec. pulse of 1.0 mAmp., applied to the occipital lobe, or 0.1 mAmp. to the region of periaqueductal gray and the third nerve nuclei, elicit a CR in the monkey. There is no reason the same should not be true for man, and it will be of great interest to see what relation such evoked, "learned" neural activity bears to conscious processes.

From these diverse facts, as discussed elsewhere in more detail,[5,6,9,11] it is possible to imagine that the basic factor in the formation of conditioned reflexes is a change in the threshold of a subcortical neural hierarchy controlling the complex conditioned movement. The existence of such controlling hierarchies at subcortical levels is well documented. These hierarchies range from the scratch reflex and stepping movements at spinal levels to postural, righting, and attitudinal reflexes organized in the mesencephalon; or the chewing, licking, and swallowing reflexes of the mesencephalon and medulla compounded in the feeding patterns elicited by hypothalamic stimulation. It is probable that some of the hierarchies controlling conditioned movements have a cortical link in their organization, or that cortical activity contributes importantly to the threshold shifts in the controlling neurons. An example of the latter action may perhaps be seen in the experiments of Rusinov[22] and of Morrell, reported in this volume, whereby the polarization of the motor cortex so alters the threshold of a particular movement complex that it can be elicited by photic or auditory stimuli. Possibly in an analogous fashion the application of a CS anyplace in the nervous system contributes sufficient additional excitation to the neurons controlling the conditioned movement (whose threshold has somehow been lowered by training and the experimental situation) to trigger the CR.

The evidence cited above points to the importance of subcortical elements in CR elicitation. Much or most of the organization of movements occurring to

cortical stimulation must arise in subcortical hierarchies. Production of an integrated movement by cortical stimulation would be unlikely if the organization were effected at the cortical level. The stimulating current should disrupt any normal processes of integration inherent in the stimulated cortex, yet integrated movements can be elicited. A movement of the hand up, opening the mouth, and retraction of the tongue occurs often in infants at the "oral stage." A highly similar movement pattern of mouth and arm can be elicited by stimulation of the monkey precentral gyrus[6,11] or rhinal fissure.[3] This shows that a naturally occurring primate movement pattern can be elicited by presumably disruptive cortical stimulation and, as in the case of other movements "inherent" in cats[11] and of similarly conditioned movements in cats, dogs, and monkeys, this pattern can be elicited by stimulation at more than one location. One cannot easily believe the movement to be organized at each location of the stimulating electrodes.

Furthermore, as shown by Loucks[15] and confirmed in our experiments on monkeys, the movement elicited by cortical stimulation can be altered by training; indeed, as is obvious from the above, through conditioning procedures stimulation in any selected cortical area can elicit the same (conditioned) movement. This holds true even for the monkey precentral gyrus, in which stimulation that inherently yields an arm flexion can, after training, produce an extension. (Actually, however, the situation is not this simple, since stimulation of the precentral gyrus will still produce arm flexion after training if the current is increased.) The extensor movement is elicited with currents too low to elicit any inherent movement, and one is tempted to say in subjective terms that the perceptual or sensory threshold for the "motor" cortex is lower than that for eliciting movement. Nevertheless the motor system inherently activated from this area is also being affected by this low, tetanizing current, since it is thrown into immediate action by a loud, unusual noise or, especially, by a painful stimulus. The effect of the latter completely overwhelms the conditioned extensor movement and the cortical stimulus, previously subliminal for the inherent movement, then sums with the painful input from the tail to produce arm flexion of convulsive intensity. Again it seems unlikely that the neural site of this convergence of excitation applied to tail and cortex is beneath the cortical electrodes.

The painful stimulus brings into play complex emotional factors that might underlie this augmentation. Our Soviet colleagues[21] caution us that in the use of these concepts of emotion and motivation we take care to avoid the implication that it is the concomitant psychic activity that influences the neural outcome. To the materialist, however, this is a completely artificial problem since the psychic activity is but a manifestation of neurons and hence, obviously cannot interact with them. In speaking of neural behavior in which the complexity of action lies beyond our present capacity to analyze it, I see no prejudice whatever to the materialistic argument to speak of these behaviors in terms of their probable psychic manifestations, of the totalized and integrated neural pattern. Naturally this adds nothing to our understanding of the neural basis of this activity, but it is nevertheless useful in that it enables us to describe and think about this activity in common sense terms and to keep before us a problem of major importance in behavioral neurophysiology.

Certain forms of neural activity, inherently rewarding or punishing, pleasant or unpleasant, positively or negatively reinforcing or motivating, or biologically significant, are able to organize the entire motor apparatus into activities of approach or avoidance and to exert great influence upon the systems operative in memory and learning. MacLean[16] has emphasized that the limbic system is the seat of this motivational activity, and Olds[19] and Lilly,[14] among others, have further confirmed this by using the animal's reaction of starting or stopping trains of electrical stimuli in these regions as an index of inherent motivational connections. There is some danger, of course, that the self-stimulation achieved in such procedures is an experimental artifact resulting from the confusional effects of electrical stimulation of the limbic system. In most instances a much higher intensity of current is required for self-stimulation than for elicitation of defensive CRs[5,17] or of arousal (Olds, cited by Doty[4]) from the same point, and electrical abnormalitites are often induced by this high intensity self-stimulation.[5,20]

Sometimes, however, very low intensities are able to maintain self-stimulation (Olds and Lilly, cited by Doty[4]), and there is no a priori reason why one should not be able, with an electrical stimulus, to enter positively motivating systems. Of 21 cats tested in our laboratory[5,17] (unpublished data) with electrodes in 70 points, primarily within the limbic system, aversive effects seemed predominant. Self-stimulation was obtained from only 13 locations, whereas stimulation at another 37 positions was avoided. The lowest threshold found for self-stimulation was 0.5 mAmp. for a 0.5 sec. train of 0.2 msec. pulses at 300 pulses/second in cats 370 and 438. In cat 438 the electrodes were aimed at the anterior commissure and in cat 370 at the anterior ventral nucleus of the thalamus. Self-stimulation rates in both animals were higher with 1.0 to 1.5 mAmp. In cat 438 the threshold subsequently found for eliciting a flexion CR was 0.4 mAmp. In each case the self-stimulation was abruptly slowed or halted when a moderately aversive stimulus of similar timing followed or preceded the 1.0 to 1.5 mAmp. rewarding stimulus by a few tenths of a second. Thus the self-stimulation seemed to produce neither "confusion" nor automatic, driven behavior.

A threshold of 0.5 mAmp. for self-stimulation at rates of 1000 presses/hour, comparable to those for cats 370 and 438, was also obtained in one cynomolgous monkey, not from the limbic system but from electrodes histologically localized in the right inferior pulvinar and brachium of the superior colliculus! The animal could be awakened by a stimulus train of as little as 0.2 mAmp. Each stimulus burst at the 1.0 to 1.5 mAmp. level usually employed for self-stimulation made the eyes flick about 30° horizontally to the left. Light flashes evoked potentials in this region and, if the animal was in the dark, single electrical pulses elicited potentials in the ipsilateral occipital lobe; yet the animal would not self-stimulate while in the dark. If bursts of stimuli were administered in rapid succession while the experimenter was with the animal, its eyes shifted each time under the influence of the stimulus but were immediately brought to bear again as though its attention was undisturbed. Thus, in this case too, it seems safe to surmise that the self-stimulation somehow produces satisfaction rather than confusion, but the nature of satisfaction from stimulation within

the visual system is presently as indescribable in neural terms as is an esthetic experience.

In addition to its usefulness in studying motivational systems, the self-stimulation procedure is equally important in showing that stimulation of many regions of the nervous system, particularly the cerebral cortex, is without motivational effect. Thus Giurgea and I[11] were able to show during our brief opportunity to work together that the cortical stimuli he used as both CS and US to establish behavioral CRs[12,13] were without effect on the animal's behavior in a self-stimulation situation. In other words, by his technique of cortical-cortical stimulus pairing, conditioned reflexes of the usual behavioral type can be formed with stimuli that lack any demonstrable motivational component. The conditioning mechanism per se may thus operate independently of the motivational factors that are unavoidable in most behavioral conditioning procedures. The motivational component, however, probably plays a very important role when it is present.

Direct comparison of the motivated versus nonmotivated reflexes has thus far been made in one monkey. In this instance a CR of arm flexion was established by pairing stimulation of the visual cortex as CS with stimulation of the motor cortex as US.[11] The animal in the self-stimulation procedure was entirely indifferent to these stimuli. The threshold for CR elicitation from visual cortex stimulation was 0.55 mAmp. in this nonmotivated situation. The same visual cortex CS was then paired with an electric shock to the tail, which could be avoided by a lever-press during the CS. After training with this highly motivating US, only 0.2 mAmp. was required for stimulation of the visual cortex to elicit a lever-pressing CR. The motivational system can be inferred to be responsible for this altered threshold for effective cortical stimulation and, in addition, is probably also operative in shifting the elicited movement from flexion to extension in the absence of any specific movement pattern imposed by the US.

In summary, subcortical systems predominate in effecting the attentive and motivational components so important in most conditioning. A major portion of the motor system representing the conditioned reflex itself may be organized subcortically and be the site of the principle change in excitability resulting from the conditioning process. The cortex in such a scheme would contribute to the motor organization and the background shifts of excitability in the conditioned system, but would serve principally as the analyzer of the sensory inputs. Beyond stating that both cortical and subcortical elements when present must always be involved in conditioned reflex formation, the available data and our understanding of their significance are still too vague to support much specific speculation on what is occurring in this complex process.

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UNIDIRECTIONAL RATE SENSITIVITY: A BIOCYBERNETIC* LAW OF REFLEX AND HUMORAL SYSTEMS AS PHYSIOLOGIC CHANNELS OF CONTROL AND COMMUNICATION†

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Introduction

In the study of the behavior of biological systems, the most obvious relations to be considered are those where a response bears some quantitative relation to the intensity of stimulation. The relation between the quantitative measure of the response and of the stimulus is generally monotonic, that is to say, if the response is in a positive direction for increasing stimulus intensity, this is true regardless of the level of intensity at which the system operates. Whether this monotonic relation be approximated by a logarithmic or a power law as is being debated for psychophysiological measures, or some other linear or nonlinear function, it may be said that in such systems a monotonic relation is sought between the quantity of a stimulus and quantity of response.

A system where such a relation exists can be said to be sensitive to the *amount* of a stimulus. Most physiologic research has been concerned with the evaluation of this kind of sensitivity. We shall call this relation of stimulus and response "proportional" sensitivity without meaning to imply, thereby, that a linear response characteristic is involved. There exists, however, in physiologic systems, a frequently found sensitivity to the *rate* of change of the stimulus rather than its (steady state) quantity. Wherever, sometime after a change of the stimulus to a new level, the response no longer indicates what this change in level was, rate sensitivity is involved. This "forgetting" of quantitative levels of stimulus, in many instances, is called "adaptation." Adaptation, however, is not in this sense an active process. It is merely a *lack of continuing information* about the level of the stimulus. Rate sensitivity often exists where adaptation is not commonly thought of (for example, the baroreceptors in the carotid sinus are known to be rate sensitive). In a system with rate sensitivity, information is transmitted about the rate of change, and also (if the response of the system is slow compared to the change in the stimulus), about the *extent* of change. Sometime after a change to a new level has taken place, a system with rate sensitivity only does not remember the change. That means that the response of the system, sometime after the change, is zero although the changed level in the stimulus persists.

A graph of a typical rate sensitive response to a step change in stimulus is shown in FIGURE 1. The return to zero level is a function of the dissipative elements of the system and may be described by a time constant. The peak of the initial spike is related to the intensity of the stimulus monotonically as for "proportional" sensitivity.

* Biocybernetics denotes the dynamic study of autonomic and humoral physiologic control systems, that is, those biological control functions that operate without conscious awareness. It may be regarded as a branch of physiology.

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Many systems have an additional integration time constant in their response that does not allow time to rise as steeply as in FIGURE 1. Such systems respond to a step change as shown in FIGURE 2. A response of this kind indicates the presence of two dissipative time constants such as, for example, a

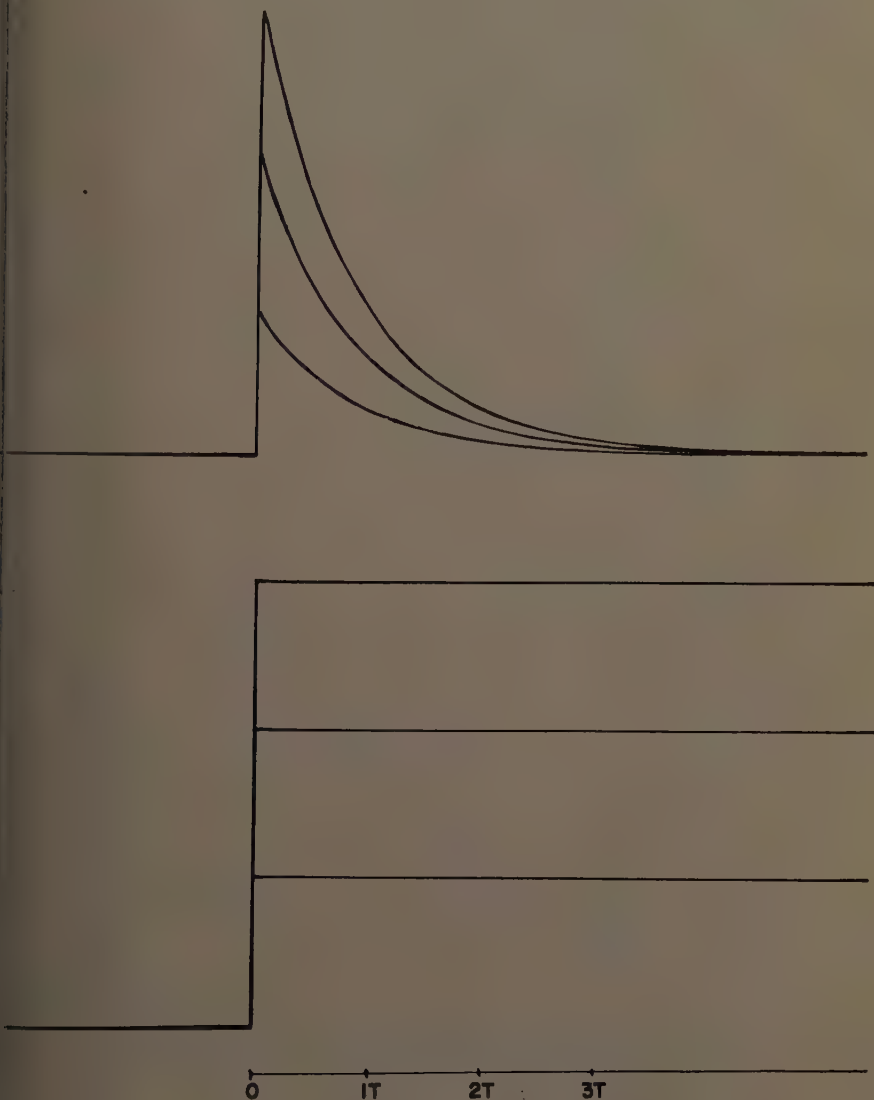

FIGURE 1. Responses to step stimulus changes of 3 different amplitudes of a system with rate sensitivity only. The rise of the step is assumed to be fast compared with the rise in response of the system. Note that for this condition a rate sensitive system *does* transmit information about the quantity of change. The height of the peak is proportional to the height of the step change. The information transmitted is transitory in nature, the decay of the response is exponential for the simplest transfer function, $\frac{s}{1 + Ts}$.

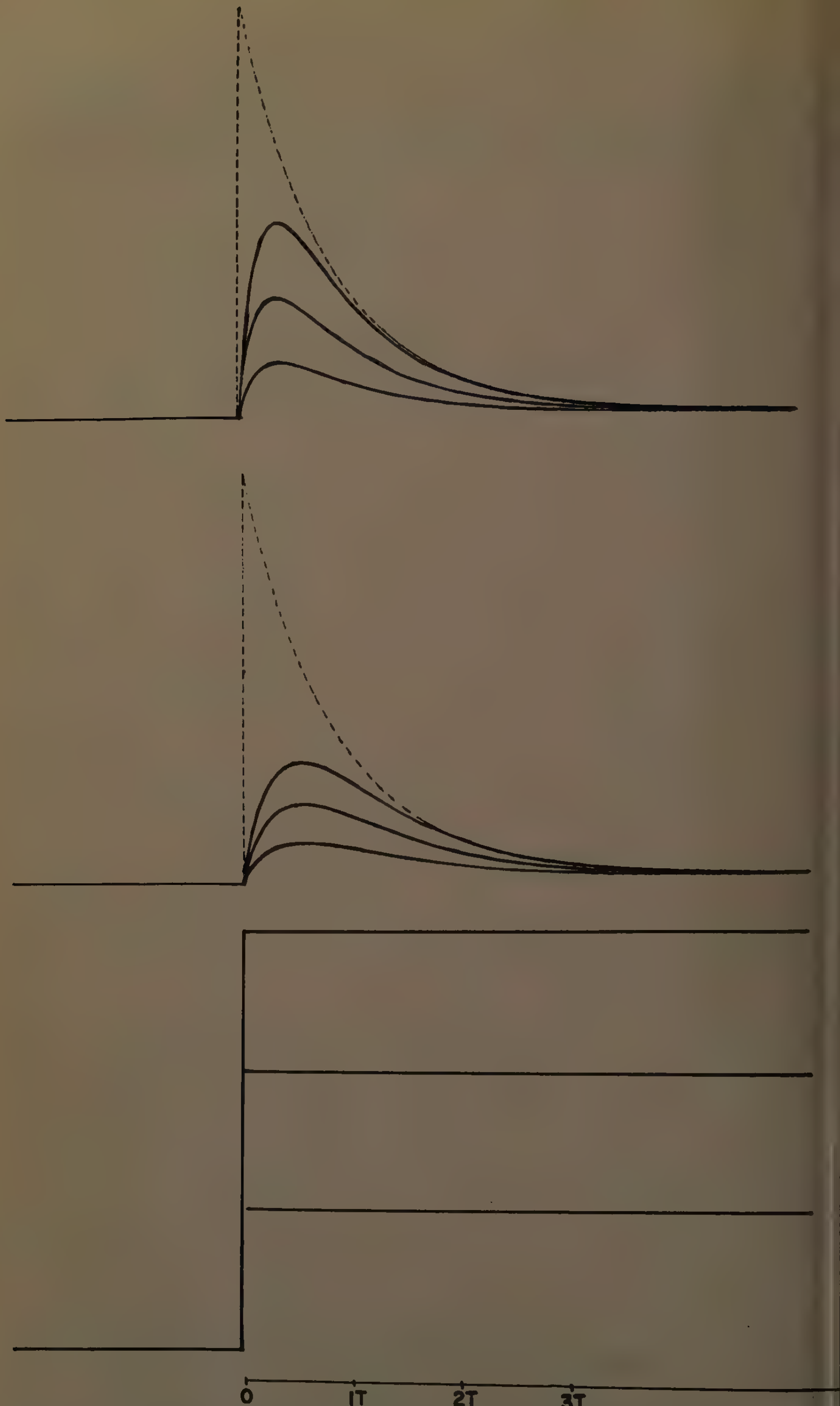

FIGURE 2. For a rate-sensitive system that has a response lag (not a transportation lag
of comparable magnitude to the decay time constant T, the sharp rise of the response to step

three-compartment diffusion system where diffusion takes place from compartment A to B and then from B to C (a three-compartment chemical reaction system or, more generally, an energy storage element system with two independent energy storage elements functions similarly).

Rate sensitivity thus implies a response of finite duration that also is a measure of the extent of the change, as contrasted with the "proportional" response, where information about the change in stimulus continues to be expressed as an indefinitely held change in the level of the response.* Many biologic systems have combinations of "proportional" and rate sensitivity. Nevertheless, in many instances, distinction between the two kinds of responses is not made.

It is the purpose of this paper to point out many interesting consequences that occur when biological limitations are placed upon the rate-sensitive responses without corresponding limitations on the "proportional" sensing. That these two aspects of information communication might be subject to different independent influences is perhaps not surprising, although it has been little investigated. However it is of considerable importance that there is encountered a basic structural limitation in rate-sensitive communication possibilities in biological systems. It will be shown that an inherent thermodynamic limitation does, in fact, exist on the rate-sensitive aspects of biological control systems, making it possible for a single channel of information to be sensitive to rate of change in one direction only.

Unidirectional Rate Sensitivity

Unidirectional rate sensitivity was first experimentally discovered in a number of biological reflex systems that will be described later. Upon further thought, however, this property appeared to have a fundamental cause in the very nature of the biological channels of communication. Unidirectional rate sensitivity (URS) came to be seen as a necessity and consequence of biological existence. It is different from a structural law such as the biologic law of cellular structure in that, although its causes lie in the biological structure, its effects are seen under dynamic conditions only. It is therefore appropriately called a biocybernetic law since it pertains exclusively to the manner of possible dynamic change and transmission of information and control.

If we consider a single channel of biologic information transmission—for example, a single stimulus receptor situation where the receptor is linked to a communicating nerve path to the brain—it is clear that at one or more places

* Stimulus and response are used here as synonymous to input and output, respectively, of a dynamic system.

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input changes is mollified, and the characteristic response shapes are as shown. The dotted, sharply peaked response is the form of the response that would exist if it were not for the extra integrative time constant. The form of the transfer function for this type of response is

$$\frac{s}{(1 + T_1 s)\,(1 + T_2 s).}$$

Two sets of responses are shown: (*top*) $T_1 = T_2$, (*bottom*) $T_1 = 2\,T_2$. Elements of this type of response shape are commonly found in biological responses such as the pupillary light reflex, the GSR reflex and salivary flow reflex. Systems with unidirectional rate sensitivity and with this type of transfer function show these response shapes for impulse stimuli in both directions, as well as for step input change in one direction.

in this transmission chain, the information is transmitted via a chemical substance where concentration of this chemical substance represents the information conveyed. It is clear that at such a point in the transmission chain the concentration of chemical A has to fluctuate in accordance with the information transmitted. Another way of saying this is that the chemical concentration of substance A is an analog of the information received from the stimulus.

Thus if the information is to be the rate of change of the stimulus, then the chemical analog will have to represent rate of change of the stimulus. It will be clear at once that certain difficulties arise as a result of this. For example, if we think of a container of water into which we drop salt in response to a change in stimulus, it will be seen that it is easy to increase the concentration of salt in the container by dropping salt into it. Should a stimulus of change in the opposite direction occur, the response would have to be the corresponding reduction in salt concentration in the container. While it was easy to increase the concentration rapidly by throwing in salt, what means can be employed to decrease the concentration rapidly without the use of other chemicals?

If we admit that somewhere along the transmission chain chemical concentration has to follow the fluctuations of the information, then we may consider what limitations, if any, are present on the way in which this fluctuation can be a faithful representation of the required information.

Let us then consider the possible ways in which chemical concentration within the path of a biological information transmission channel can be altered. We may take three cases as typical.

The release of the chemical from a gland or similar structure where the release is effected through contraction of the containing walls of the storage compartment, which we shall call compartment A. In effect, the chemical A is introduced or "squirted" from compartment A at a high concentration into compartment B where the chemical concentration level is the analog of the information. The concentration of chemical A in compartment B is generally at a considerably lower concentration than in compartment A. From compartment B the chemical A is metabolized and the rate of disappearance of the chemical A from compartment B is a function of the metabolic agents and clearance rates from compartment B.

For a steady level of concentration A to exist in compartment B, the inflow rate must equal the total outflow rate. That is to say, the inflow rate must equal the sum of the metabolic and clearance rates. If the inflow rate is diminished to zero, the concentration level in compartment B will drop at its maximum rate. There is no way of increasing that rate further, other than by the action of a second chemical C, which may be excreted from a second glandular structure or otherwise produced and which acts to metabolize or to inhibit the action of chemical A. Such release of a second chemical must be regarded as a second channel of communication and therefore represents a situation that lies outside our consideration.

A rapid increase in concentration in compartment B may be effected despite its outflow time constant by a rapid infusion of chemical A. The rapidity of the infusion above the maintenance level of the previous level of concentration determines the rapidity of increase in concentration. There is thus a direct correspondence between the rapidity of infusion and the rapidity of a rise in concentration. If, on the other hand, the infusion rate is decreased, and even

shut off completely, the rate of diminution of the concentration in compartment B is limited by the outflow time constant. If this is slow compared to the rate of change of information transmitted, it is clear that the concentration will not be able to follow the rapid changes required of it equally well in both directions. It is clear that in order to do this it would be necessary to infuse a *negative concentration of chemical A*, an obvious impossibility. We therefore are faced with a limitation not present in electrical information transmission systems, where positive and negative analog quantities can be transmitted with equal dynamic response characteristics.

The fact that negative concentrations of chemicals are impossible, places a limitation on the dynamic characteristics of information transmission systems that use chemical concentration as an analog of the information transmitted. Communication theory was developed primarily for electrical systems, hence the existence and consequences of this biologic communication characteristic remained to be explored.

This limitation on *rate* of change information is thus analogous to the action of a rectifier, a diode, or a flap valve that allows passage of a quantity in one direction only.* This means that although proportional information may be transmitted readily by the chemical analog, rate sensitivity can be transmitted only in one direction: that of increasing chemical concentration. Whether this increasing chemical concentration means an increasing rate or decreasing rate of stimulus depends on the configuration of the system.

Consequently, in order to transmit rate information equally in both directions of change, two separate biological channels of information transfer are necessary. The situation here is rather similar to the necessity of two sets of muscles, agonist and antagonist, for effecting movement in either direction.

This is not a steady-state limitation, as under steady-state conditions the level of concentration in compartment B may represent changes in both directions, since there is no requirement that constrains the zero information axis to correspond to zero concentration. A step change in information with "proportional" sensing results in an increased infusion rate that raises the concentration in compartment B to a new higher level in a time determined by its clearance-time constants. The same but inverse time course occurs in a step decrease of a stimulus. This is no longer true where rate sensitivity is involved. The asymmetry of the zero level necessary to accommodate the rapid injection of chemical A as well as a rapid cut-off of an equal quantity for an opposite information transfer and the continuous rate of infusion necessary to maintain it is far too great to be practicable.

Thus, in response to a step change in stimulus, the rate of production of a chemical might respond, for example, as in FIGURE 1. This means the rate of production will increase and gradually adapt back to its initial value. The total area under the curve indicates the amount of chemical which is produced by the indefinitely held step change of the stimulus, and is thus a measure of the change

An equal step of the stimulus in the opposite direction would have to result

* As in a diode, the rectifying action may be slightly imperfect, depending on steady-state levels of concentration, but the asymmetry observed is clearly the result of a rectification process.

in an equal negative amount of chemical introduced into the system. This would be possible only if the resting rate of production of the chemical—that is, the rate of production when no change occurs—would be sufficiently high to allow a diminution of the rate of production to be equivalent to the introduction of a negative amount of the chemical. This is unlikely for three reasons: (1) the relatively large dissipation required for no information transfer, that is, for zero change; (2) the greatly reduced sensitivity that is a consequence of a high resting rate of production; (3) since it is important for the system to be informed about the direction (or sign) of the change, a substantial resting level would require a stable comparator to be available elsewhere in the system, any slight fluctuation of which would cause rate sensitive stimulation of erroneous direction as well as magnitude.

Mathematically, a rate-sensitive sensor performs differentiation. The output of a purely rate-sensitive sensor therefore should be zero when no change is taking place. A continuous level of activity would make it much more difficult for the organism to distinguish between no change and a change, since only an incremental change in output is produced. It should be emphasized that these considerations do not apply to the "proportional" sensing elements, or to the "proportional" part of a combined proportional and rate sensitive element, the activity of which varies "proportionally" with the level of stimulus. Unidirectional rate sensitivity is thus in this sense a considerably more efficient and sensitive means of information transfer, in biologic systems.

The problem of how the organism combines rate-sensitive and proportional information is an interesting question raised by these considerations. It would seem that these two different dynamic measures may be handled with separate information transfer systems by the organism: two channels for bidirectionally rate-sensitive information and at least one channel for "proportional" information. How these channels are further "interpreted" by the nervous system is a question raised for investigation. Since rate sensitivity is often associated with the concept of anticipation, it may be said that anticipatory responses are possible in a single channel only for changes in one direction.

A second way in which chemical concentration can be changed in a compartment is by altering the rate at which a chemical is created at the sensor or elsewhere in the communication link. Thus, for example, acetylcholine is produced at the nerve synapses and facilitates transmission of impulses in a way that may be described as a digital to analog and analog to digital conversion. That is to say, the firing rate entering the synapse produces acetylcholine in quantities "proportional" to the firing rate. The concentration of acetylcholine in turn "proportionally" affects the firing rate of the outgoing firing rate. Should the incoming firing rate cease completely, the concentration of acetylcholine will diminish at its maximum possible rate, provided the other factors affecting its production and destruction, such as cholinesterase or adrenaline remain, at the same time, unaltered. Therefore the same considerations apply as in the first-mentioned situation.

A limitation, although of a somewhat different kind, also exists in the repetitive firing of a nerve or a receptor organ where the steady-state rate can be diminished to zero but no further. However, here the steady-state firing

rate is frequently sufficiently elevated to allow rate information in both directions to be transmitted to some extent.

A third possible method for changing concentration of a chemical is through diffusion only from one compartment to another through a membrane or orifice. Diffusion may be either passive or active, unidirectional or bidirectional. For passive diffusion equilibrium states are achieved that depend on the relative infusion and clearance rates. It is thermodynamically impossible for a chemical to proceed from a less concentrated to a more concentrated state. Thus, for example, a chemical flowing from a narrow orifice into a wider chamber undergoes a dilution that is not reversible. It is clear that the limitations of the nonexistence of negative concentrations are also applicable for these cases. If active transport is involved, a control system that acts on enzymes or enzyme systems or other active catalytic functions can affect the system dynamics. However this again would have to be considered as a separate channel of control. For transfer through osmotic pressure it is clear that osmotic pressure could be decreased rapidly only through: (1) the addition of nonexisting negative concentrations; or (2) the action of another agent, as by dilution, for example. The former is impossible; the latter represents the action of another system.

A practical aspect of importance as a consequence of this characteristic of biological structures is that it produces particular behavior patterns that have hitherto lacked explanation and even recognition. By understanding the cause of the behavior patterns it is often possible to see order where previously explanation was lacking, to recognize information in what seemed like "noise" before, to be able to distinguish between normal and pathological reactions.

The asymmetry described by this law has, as a result, a dynamic nonlinearity of behavior pattern not perceivable under steady-state conditions. As a consequence a dynamic asymmetry in the response to a symmetric dynamic stimulus is obtained. Furthermore, repetitive symmetric stimulation will cause steady state (DC) changes in output level, related to the stimulation frequency: a type of "fatigue" phenomenon. Special forms of oscillations not normally encountered in ordinary feedback systems can result. Posing special problems for control, unidirectional rate sensitivity may in some instances be of superior character in producing control. It also invites an entire field of investigation in the mathematical theory of automatic control pertaining to such systems.

Experimental Evidence

The practical application of dynamic analysis and control-system theory (originally developed for the control of man-made machines and missiles) to the study of biological behavior has in recent times made it possible to evolve a new quantitative approach to the study of the functioning of the nervous system. By examining the relation between the dynamics of the stimulus and response by this method it is possible to obtain quantitative relations that give information about the structure and interrelatedness of components within the system concerned.[1-10]

Responses to stimuli are examined particularly as to their time course and profile. The relation between the dynamic course of the response and dynamic nature of the stimulus is investigated extensively.

Two reflexes that we have studied will be given as main examples: (1) the respiratory heart *rate* reflex, and (2) the pupillary reflex to light. Other less intensively studied examples will be mentioned.

Method of Dynamic Analysis

The method of dynamic analysis of biological control system reflex, as has been stated elsewhere, consists of the following four steps:

(1) Data are obtained from the system in ways and forms suggested by control-system theory, in order to yield maximum information about dynamic interrelations.

(2) Appropriate differential equations are established on an analog computer that represent the dynamic relations displayed by the data.

(3*a*) Generality and validity of the equations, which provide solutions for the response of the biologic system to an arbitrary input (or disturbance) are first tested by comparing predicted solutions with experimental ones, using a wide variety of inputs. (*b*) If the equations are correct, then the corresponding systems of different individuals are expected to differ only in the values of the parameters of the equations, but not in the structure of the equations. Individual differences are then describable in terms of these parameters.

(4) Predictions of structural organization and component properties may be made from the equations, combined with known physiology, and predictions are tested by appropriate experiments.

Fundamentally, the method applies the standard sequence of pure scientific method (data, abstraction, verification, and prediction).

Respiratory Heart Rate Reflex

These four steps were applied to the variations of heart rate produced by respiration with the following results summarized briefly:

It was found that the variations in heart rate produced by respiration were the result of a basic reflex that we called the respiratory heart rate (RHR) reflex. This reflex has a biphasic nature and has a duration of approximately 15 sec. The reflex is elicited when one takes an inhalation and was shown to be initiated by stretch receptors within the chest and not by hemodynamic factors. FIGURES 3, 4, and 5 illustrate the basic RHR reflex and actual and simultaneously calculated heart rate patterns produced by various forms of breathing. Through the dynamic analysis of this reflex it became possible to predict the changes in heart rate produced by an arbitrary manner of breathing. It was first noticed that expiration does not produce the inverse effect of inspiration, that the transients produced by expiration are in fact rather similar to the inspiratory ones but are smaller in amplitude and also have a biphasic nature. In more than 1000 subjects tested the biphasic nature of the RHR reflex was never reversed. There always is found first an acceleratory phase followed by a deceleratory phase.

From the mathematical analysis of these reflex patterns and experiments suggested therefrom follow physiological conclusions: (1) this reflex is initiated by stretch receptors and not hemodynamic factors; (2) these particular stretch receptors concerned are sensitive to inspiration only and not to expiration; and (3) the smaller expiratory effects were due to a different stretch receptor

and were in the same direction as the inspiration reflexes. (That a different stretch receptor is involved can be shown by the differential action of atropine in the recovery phase of the reflex.)

It became clear that the heart rate changes produced are superimposed inspiratory reflex transients, that the pattern obtained is dependent on whether sufficient time is available for each reflex pattern to complete itself before the onset of the next reflex. The correspondence of actual and predicted changes in heart rate for various kinds of breathing is proof of the correctness of the differential equations describing the phenomena.

It is important to remember that the reflex is found to be sensitive to stretch in one direction only, that is to say, it responds to rate of change in one direction only.

Pupil Reflex to Light

We shall next consider the other reflex studied, that of the pupillary reflex to light. In applying the method of dynamic analysis to this reflex, the following basic behavior patterns were found:

(1) A flash of light produces the well-known contraction and redilation of the pupil.

(2) A flash of darkness (that is, an interruption of light from a medium intensity level), contrary to expected behavior, produces a contraction and not a dilation. The contraction pattern is similar to that produced by a flash of light but somewhat smaller in amplitude.

(3) A stepwise increase in light produces a pupillary response similar to the flash response but not redilating quite to the initial level.

(4) A stepwise decrease in light produces a slow dilation.

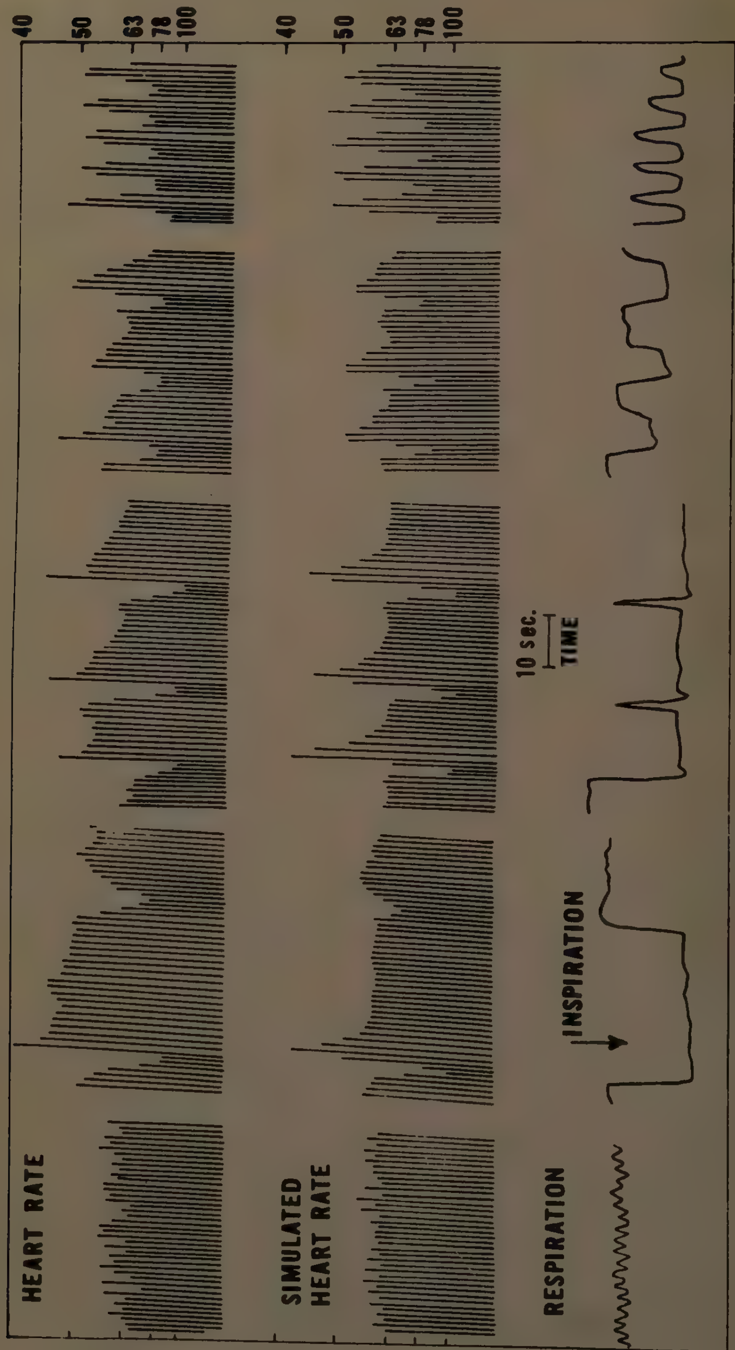
Of all the responses only the last one is monophasic, the other three are biphasic.

It was first of all necessary to explain these four patterns (FIGURE 6) with underlying mathematical assumptions that would account for all of them. It became apparent that the effect of the stimulus consisted of two aspects: (1) a function of the amount of light; and (2) a function of the rate of change of light. This second function, however, was only present for an increasing direction of light, whereas decreasing intensity produced no change in the rate-sensitive reflex response. Thus the arrows in FIGURE 7 show that the effective stimulus to the rate-sensitive reflex was only the light-increasing portions of each flash, whether a darkness or a light flash. Thus the similarity of these responses is explained.

FIGURE 8 shows experimental results for pupil responses to light flashes and darkness flashes. The flashes have been purposely extended in duration to about 0.3 sec. in order to show the latency relations clearly.

With such assumptions and corresponding mathematical equations it was possible to simulate the behavior of the pupil for various light stimuli as shown in FIGURES 9, 10, and 11. It is clear that the correspondence of the actual pupil diameter and computed pupil diameter for widely varying light stimuli confirms the correctness of the analysis.

A further interesting phenomenon that can be observed with this reflex is that the saturation level of the two sensing functions occur at different light


HEART RATE
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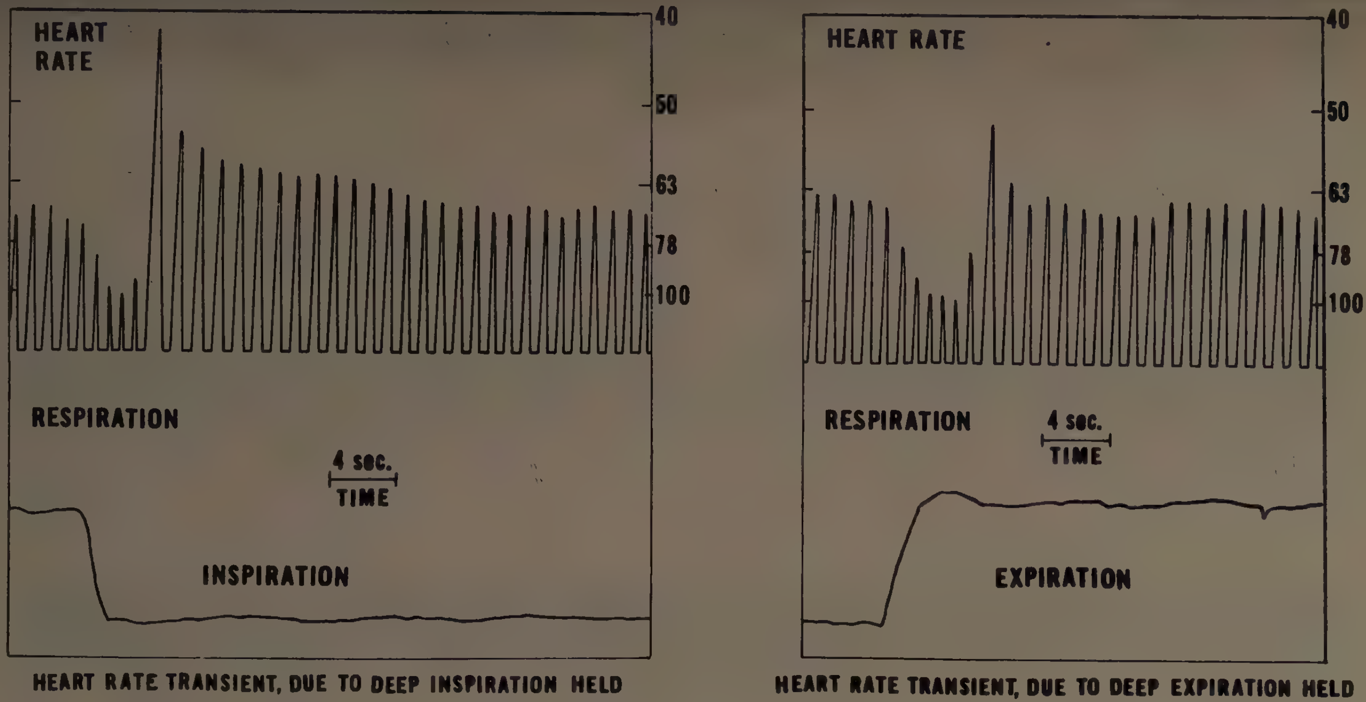

FIGURE 3. Simulated and actual heart rate patterns for various modes of breathing; basic RHR (respiratory heart rate reflex) transients are shown in lower portion of figure. Ordinates represent time between consecutive heart beats as recorded by a cardiotachometer. Subject, 26-year-old male, supine position, resting state. Amplitude of the transient is variable from subject to subject, but the basic biphasic shape remains. Reproduced from Clynes[2] by permission of *Science*.

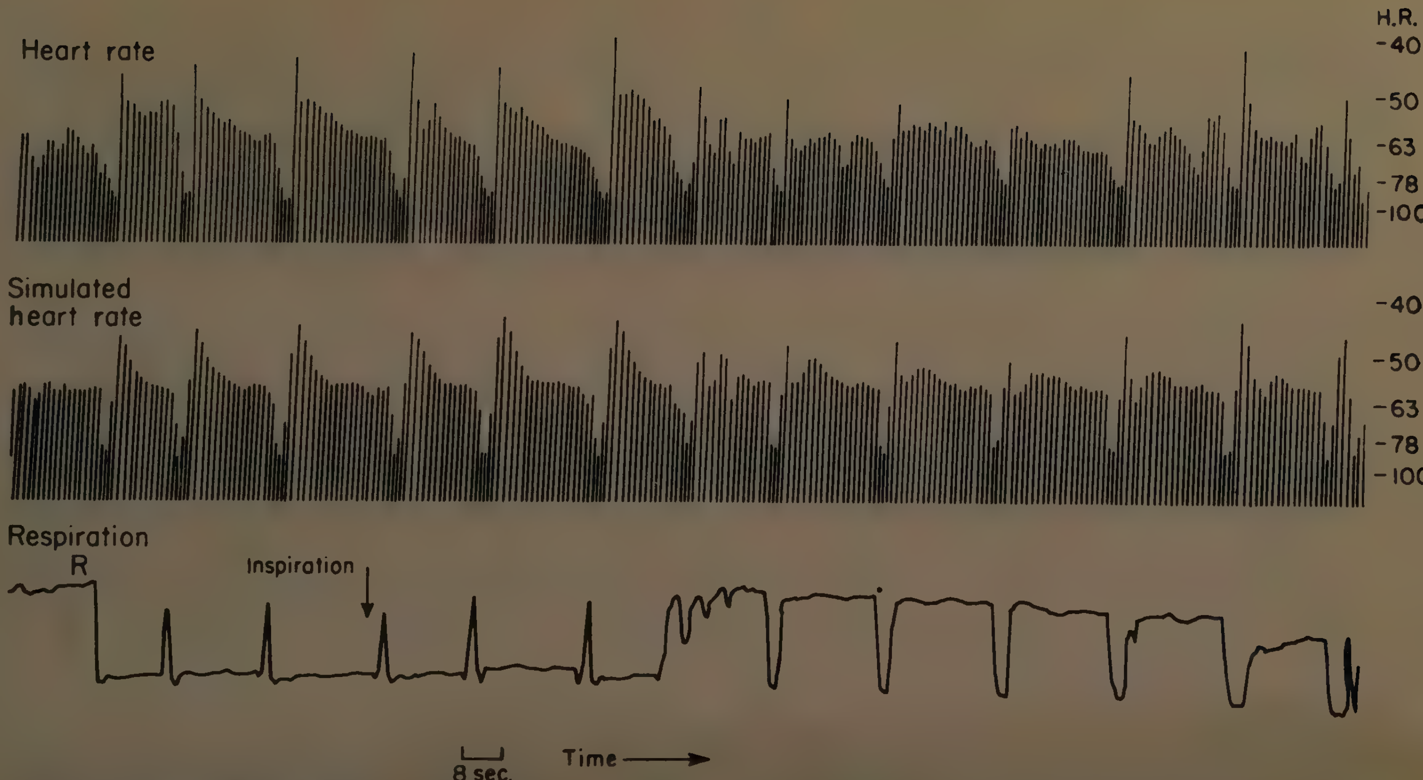

FIGURE 4. Actual and simulated heart rate transients due to negative and positive impulse breathing. This type of breathing is customary during swimming.

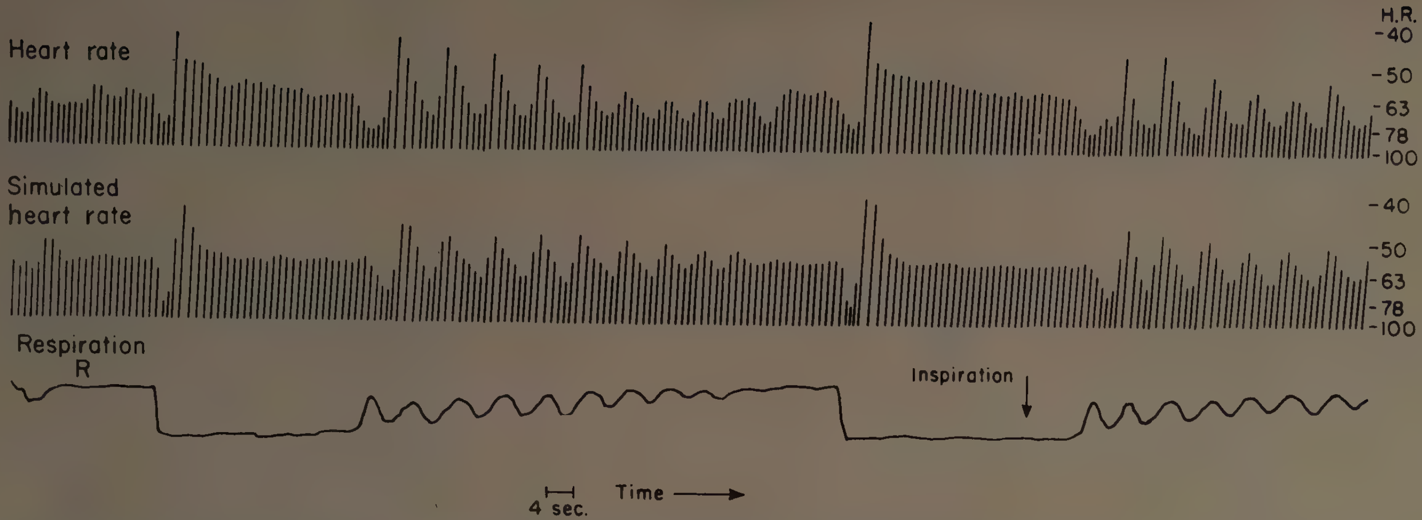

FIGURE 5. Actual and simulated heart rate changes due to normal breathing interspersed with breath holding. The differential equations describing the reflex, and the simulation shown in FIGURES 3, 4, 5, are included in the MATHEMATICAL APPENDIX.

intensities. The rate sensitive response saturates first so that with increasing level of light intensities, the proportion of "proportional" to rate sensitive response increases (a consequence of this is the so-called W response of Lowenstein and Loewenfeld).

The pioneering work of Lowenstein and Loewenfeld (to whom we are greatly indebted for permission to use their infrared pupillograph and for assistance in its use) over many years has resulted in a large store of clinical and experimental

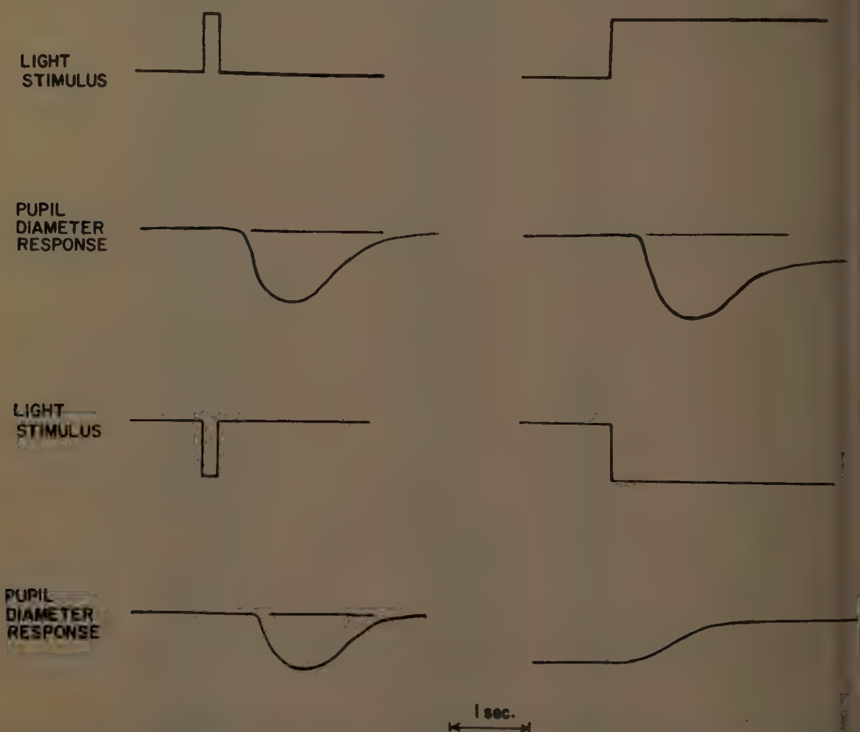

FIGURE 6. Response of the pupil to four basic types of light stimulus inputs. The top two stimuli are a light flash and a light step respectively. On the third line the light stimuli are a darkness flash and a darkness step respectively. The second and fourth line show the pupil responses to these stimuli. Pupillary contraction is a downward deflection. An upward movement of the stimulus represents light increase.

data. These data can now be interpreted as in accordance with a hypothesis that regards the biphasic rate sensitive response as parasympathetic, and the monophasic dilation as sympathetic, in nature.

We thus have two instances of reflexes whose response is influenced by rate of change. This rate of change, however, is effective as a stimulus only when it is in one direction: in the case of the RHR reflex in an inspiratory direction of stretch, in the case of the pupillary reflex to light, for increasing light.

In addition to sensitivity to rate of change of this stimulus, sensitivity may or may not exist for the amount of stimulus. Such response to steady-state stimulus quantity is present in the pupillary reflex (apart from the effects of

adaptation to light). The total response pattern is the sum of the individual contribution of rate sensitive and quantity sensitive reflex.

Tactile Information System

A third instance of an information transfer system that is capable of operating only with unidirectional rate of change is found in the sense of touch in so far

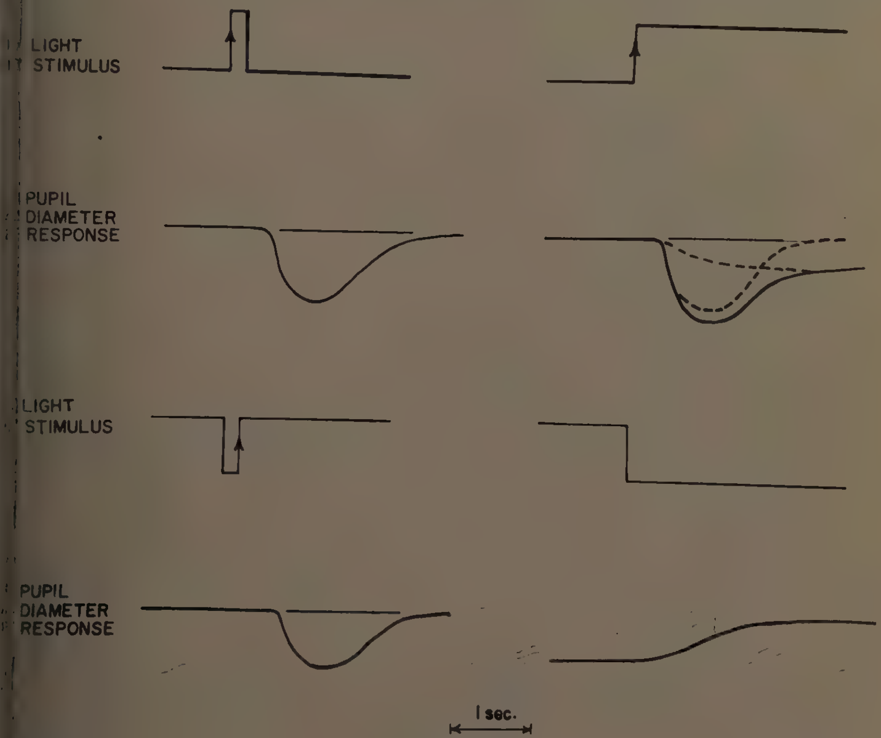

FIGURE 7. The same stimulus and response patterns as in FIGURE 1 with the addition of arrows to indicate where a stimulus to the rate sensitive aspect of the sensor is present. Rate sensitivity exists only for light-increasing rates of change. The dashed lines in the step-response curves on the second line indicate how the actual step response is the sum of two curves, namely, the rate-sensitive response curve and the "proportional" response to increased light. The response to a step decrease in light as shown in the bottom right corner of the diagram is the inverse of the step "proportional" response to increased light as shown on the dotted curve on the second line. The reason for the similarity of the light and darkness flash responses is seen in the similarity of rate-sensitive stimulus as shown by the arrows. The darkness flash response is, therefore, also slightly more delayed compared to the lightness light responses.

as pattern recognition is concerned. Touching a pattern provides information concerning the number of protuberances through the deformation of the touch receptors. After a certain time during which the receptor remains in touch with the pattern, it has adapted to this, and no longer provides information as to the number of protuberances. When now the receptor (such as a finger) is removed, the negative physical deformation provided by the act of removal does not give any new information on the number of protrusions to be

found in the pattern. Thus the rate of change to which the receptor reflexes are sensitive is only in one direction.

Experiments performed with protruding pin points confirm this. The experiment consists of touching a number of protruding pin points with the finger while the arm is supported in a steady manner. The number of pin points may be any number from 3 to 6. The subject is able to determine the number of pin points that he is touching. Pin points are chosen in order to minimize the temperature-receptive sensations.

After an interval of 2 min. at a time when the subject no longer feels the

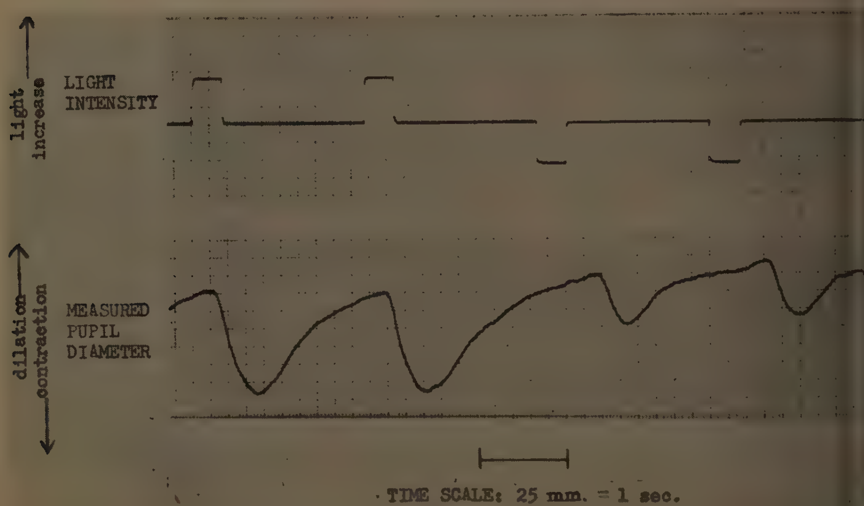

FIGURE 8. Pupillary responses to light flashes and to darkness flashes of 0.3 sec. duration showing contraction and redilation in response to light flashes, and smaller, similar responses to darkness flashes, shifted in time, however, by the width of the flash, as compared with the light-flash response. A slight initial dilatation can be noticed with the darkness-flash responses due to the "proportional" sensor. The response produced by the darkness flash is smaller for several reasons: (1) a darkness flash of somewhat smaller amplitude than the light flash was used; (2) the effects of the proportional sensor are in the opposite direction; (3) apart from the first two considerations, the sensitivity to light is also not linear.

pin points, a number of the pin points are very slowly removed; so slowly that the subject does not feel their removal. The number of pin points remaining may be anywhere from 2 to 6 (for the latter no pin points have been removed). The subject is now asked to remove his finger. The removal of the finger should be done without a sideways motion. It should be physically the opposite movement to the original touching movement, that is to say, a vertical displacement.

The subject now is asked how many pin points were present at the time of the removal of his finger. It is invariably found that the act of removal does not provide tactile information to the subject about how many pin points were present at this time. This shows that the negative deformation of the finger

does not provide information analogous to that provided by the original, positive deformation. That the reason for this is not saturation or numbness can be readily demonstrated by asking the subject to depress his finger slightly rather than remove it, or to ask him after immediate removal to touch the

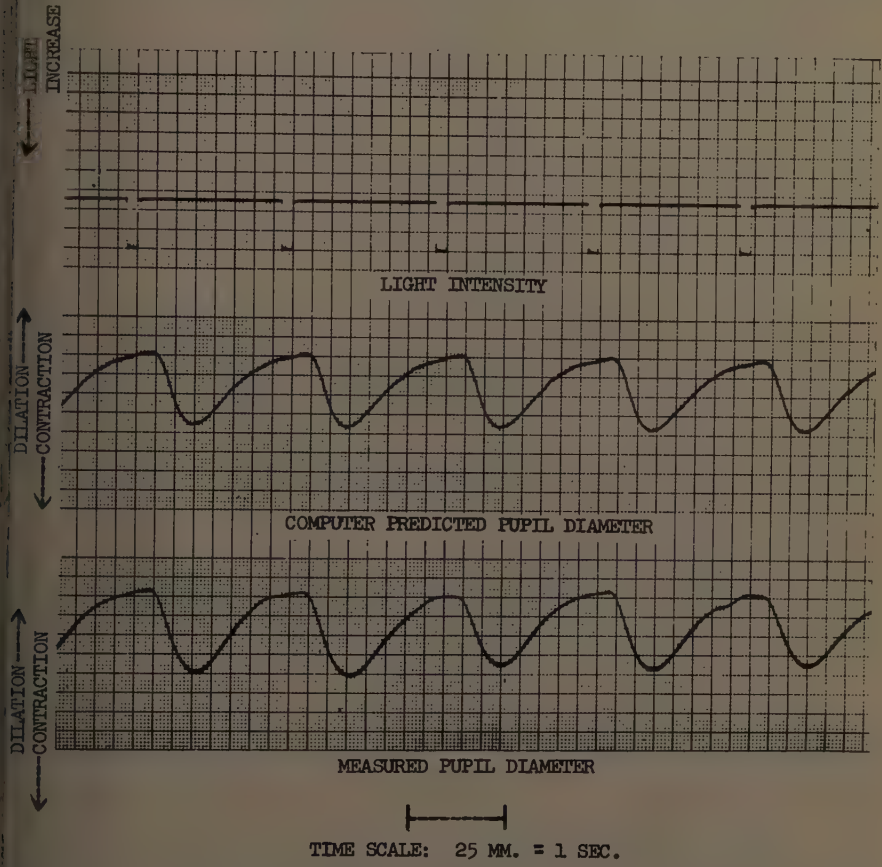

FIGURE 9. Actual and simultaneously predicted changes in pupil diameter caused by flashes of light: upper trace, light flashes at intervals of 1.6 sec. duration; downward deflection represents increase in light intensity; middle trace, changes in pupil diameter computed by the analog computer according to the transfer functions described in the text; lower trace, actual changes in pupil diameter as measured by Lowenstein pupillometer. Downward deflection in middle and lower traces represent pupillary contraction.

pin points again. In each case immediate tactile information concerning the number of pin points present becomes available.

Carotid Sinus Baroreceptor

A fourth instance may be found in the internal reflex of carotid sinus in response to variations of pressure in the carotid artery. Here the variations

in firing rate produced by variations in pressure are the sum of the response of the proportional and rate-sensitivity functions of the sensor. The rate sensitivity is, however, again only sensitivity to rate in one direction, namely that of increasing pressure, which explains that the sharp drop of pressure found during every heartbeat after the maximum systolic pressure does not produce an abrupt diminution in firing rate as would have to be noticed if the rate sensitive aspects were sensitive to decrease in pressure as well as to in-

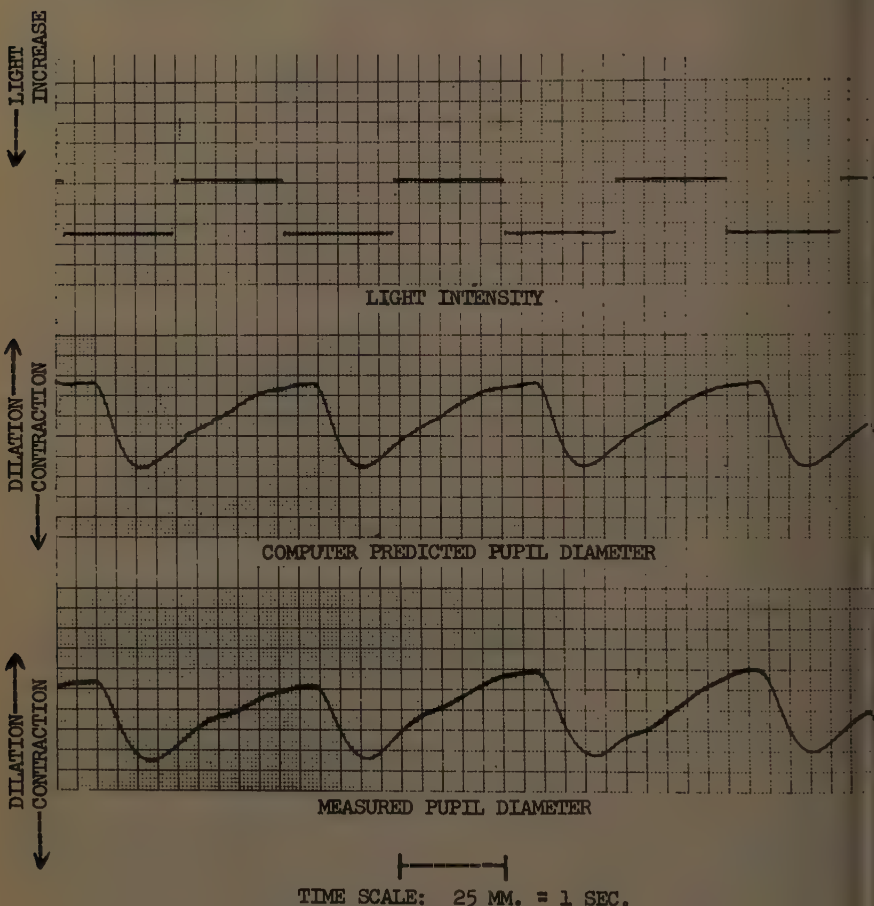

FIGURE 10. Actual and simultaneously predicted changes in pupil diameter caused by ste changes in light: upper trace, alternate dark and light steps at intervals of 1.07 sec. duration downward deflection represents increase in light intensity; middle trace, changes in pupil diam eter computed by analog computer according to the transfer function described in the text; lower trace, actual changes in pupil diameter as measured by Lowenstein pupillometer. Downward deflection in middle and lower traces represent pupillary contraction. Note th asymmetry of the response due to the nonlinear dynamic characteristics. The second portio of the ascending curve beginning with the slight break in the curve represents the dilator re sponse to the darkness step. The latency of this is about 0.4 sec. The descending part o the curve and the first part of the ascending part is the response to the light increasing step

rease. Experiments with muscle systems also reveal dynamic nonlinearities hat may be explainable by the consequences of unidirectional rate sensitivity.

If one searches for the basic causes underlying this rather unexpected form f behavior as manifested in these instances, one is led to examine the possiilities of information transfer with the limitations of structure that these

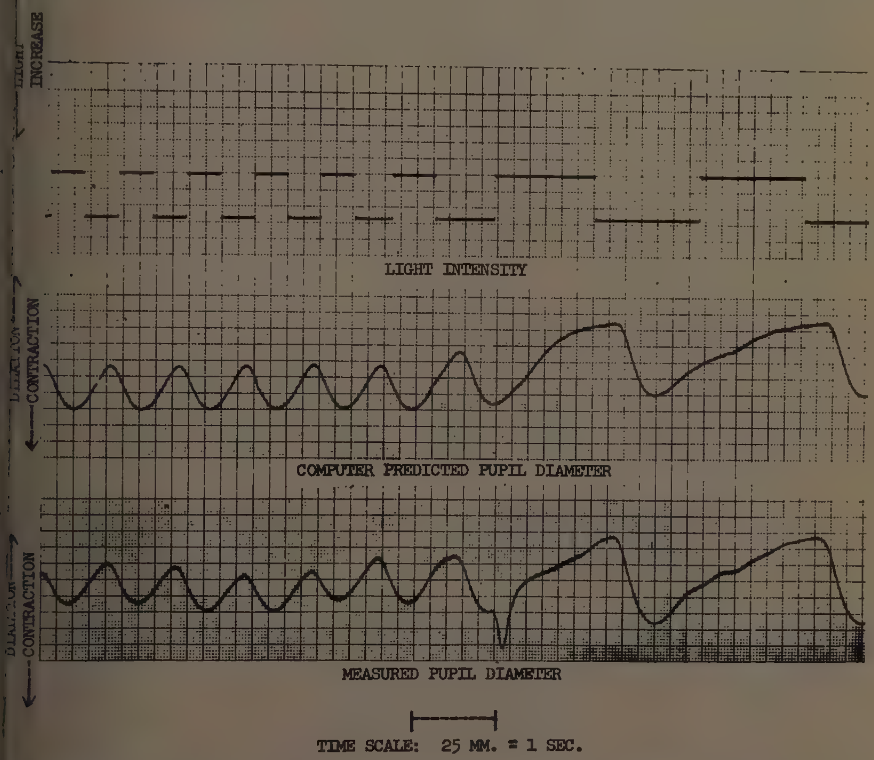

Figure 11. Actual and simultaneously predicted changes in pupil diameter caused by tep changes in light: upper trace, steps of darkness and light of varying durations; downward leflection represents increase in light intensity; middle trace, changes in pupil diameter computed by analog computer according to the transfer function described in the text; lower race, actual changes in pupil diameter as measured by Lowenstein pupillometer. Downward leflection in middle and lower traces represent pupillary contraction. The extra protuberance n the lowest trace is a blink, and is for that reason not simulated in the middle trace. The fter-effects of the blink are noticeable during the next second or so, as a departure from the hape of the calculated curve. Notice also the general shift of the pupil diameter towards a reater mean contraction as the frequency of stimulation is increased without any change in he mean illumination.

ystems possess. There exists in all these systems two basic properties that re of concern here: (1) the chemical and electrochemical nature of transfer; and 2) the unidirectional propagation of information along these structures.

Consideration of these properties led to the generalization outlined, which, n retrospect, could be said to have been evident in the first place. However, t is only through experimentation that the line of thought leading to this vas clearly established.

Conclusions

System Behavior Characteristics Arising from Unidirectional Rate Sensitivity

Following are some of the special consequences of dynamic behavior exhibited by systems with unidirectional rate sensitivity:

(1) Responses to *impulse function* stimuli of opposite polarities do not tend to cancel but tend to reinforce each other (for example, a light flash and a darkness flash both produce contraction). In control-engineering terms, the response to a doublet impulse is equal to twice the unit impulse response in the same direction regardless of the polarity of the doublet impulse.

As a result of this consequence, a response to a stimulus in such a system cannot be canceled out by a stimulus of opposite change. This means that once the response has been initiated there is no way of stopping the course of the response; it must run its course. The important implications of this behavior pattern to stimuli on many levels is obvious. It may be predicted, for example, that the response to light flash presented to one eye will not be canceled by the simultaneous stimulation of the other eye with an equivalent darkness flash: in fact, one may say there is no equivalent darkness flash, biologically speaking. In other words, the additive algebra of such biological systems does not correspond to our usual arithmetic. Thus *for impulse stimuli* the unidirectionally rate-sensitive biologic system responds in accordance with the following arithmetic, to put it cryptically:

$$2 + 2 = 4$$
$$2 - 2 = 4$$

The use of this kind of arithmetic biologically does indeed lead to interesting consequences!

The invariant direction of deflection of the GSR reflex is another example. A GSR response of opposite polarity to that normally seen has never been observed.

An example on another remote level may be given as the fright reaction to sudden danger, as in a near-miss accident where the fright reaction runs its course after it is obvious no danger is present.

(2) Interrupted stimulation of the same intensity as a similar continuous or slower stimulation (up to a certain frequency) will tend to produce a greater mean response. Thus, for example, a repeated square wave light stimulus at 3 stimuli per second produces a greater mean contraction (sometimes called tetanic contraction), than a continuous light stimulation of the same intensity or than a similar stimulation at 1 stimulus/sec. The reason for this type of behavior lies in the rectification process involved in the rate-sensitive function. The result is a DC component which is frequency-sensitive. At a sufficiently high frequency, however, the rate-sensitive response can no longer follow the frequencies of stimulation due to an integrative time constant usually present. Such behavior is also shown by the pupillary reflex to light, although the integration time constant involved here is not necessarily the same as that of visual fusion.

The GSR response also exhibits a shift in the value of resistance with frequency of response. The behavior of systems that include Pacinian corpuscles and of muscle systems tend also to exhibit aspects of this behavior; however much further investigation is required.

The investigation of fatigue as a phenomenon related to unidirectional rate sensitivity suggests itself, in reference to the DC shift with frequency of stimulation.

(3) Unidirectional rate-sensitive systems can exhibit self-sustained oscillations due entirely to this property. For example, the pupillary oscillations produced when a spot of light is placed at the edge of a pupil are due to the biphasic rate-sensitive response. This can be readily understood by observing that the redilation of the pupil is largely a part of the rate-sensitive response to the light stimulus, and not a response to darkness. The nature of these oscillations is quite different from that of the usual continuous feedback system oscillations. It is characterized by the fact that a major part of the oscillation is a passive transient during which no stimulus is active. Thus the oscillations are similar to relaxation oscillations with the difference, however, that the passive phase is biphasic as compared with the uniphasic passive phase of relaxation oscillations. The frequency of these oscillations is a function of the time course of the passive transients, and is influenced only to a second order of magnitude by the intensity of the stimulus or gain of the system.

(4) With symmetric inputs a system with unidirectional rate sensitivity will show asymmetric output shapes. The asymmetry is a function of the frequency of the stimulus. Thus if Fourier analysis methods were to be used, a large second harmonic component would be noted, but the amount of second harmonic present would be related to the frequency of stimulus, not amplitude. It is thus not a steady-state nonlinearity but a dynamic nonlinearity that is to be observed. It is clearly important to distinguish between steady state and dynamic nonlinearities of behavior. This dynamic asymmetry is observable in addition to the DC shift with frequency referred to in No. 2.

These properties, specific to systems with unidirectional rate sensitivity, cannot here be described in mathematical detail. It is clear however, that these properties play an important role in the behavior patterns of many biologic systems. While it is possible that they may not apply to many biologic systems, it seems advisable to bear these properties in mind when investigating the dynamic and static properties of biological systems.

The information transfer limitations described by the law of unidirectional rate sensitivity are not limited to reflexes originated through external receptors. These limitations should apply equally to internal reflex functioning and communication systems. Like physical laws of motion, the law helps to ascribe causative behavior to complex patterns of observation. As a biological law, it merely expresses the consequences of structural relationships to be found in biological systems.

It remains to be emphasized that the application of dynamic analysis and cybernetics to organic systems does not imply a mechanistic view of life but, while helping to unravel the complexities of control in the hierarchy of control systems, the ultimate sources of control remain, as before, a mystery.

Mathematical Appendix

In the text of the paper considerations leading to formulation of the b cybernetic law were sketched. Here the mathematical formulations are sum marized. For more detailed mathematical analysis of the heart rate a pupillary reflexes see Clynes.[3,6]

(1) The Law of Unidirectional Rate Sensitivity states that for a single r ceptor stimulus-response system

$$y = xf_1(y, \dot{y}, \ddot{y} \cdots, x, x, \ddot{x} \cdots) + \Omega \dot{x} f_2(y, \dot{y}, \ddot{y} \cdot\cdot x, \dot{x}, \ddot{x} \cdot\cdot)$$

where x is the input (stimulus)

y is the output (response)

Ω is an operator defined by the following

$$\Omega = 1 \text{ when } \frac{dx}{dt} \geqslant 0.$$

$$\Omega = 0 \text{ when } \frac{dx}{dt} < 0.$$

(2) The respiratory heart rate (RHR) reflex is mathematically defined follows for the inspiratory reflex

$$\frac{\mathcal{V}}{\mathcal{R}} = \Omega \frac{-ks^2}{(1 + T_1 s)(1 + T_2 s)}$$

where $\mathcal{V}$ = the Laplace transform of the pacemaker inhibition
$\mathcal{R}$ = the Laplace transform of the respiration (thorax circumference)
s = the Laplace operator
k = a sensitivity constant
T_1, T_2 = time constants

and

$$\frac{1}{4\pi^2 r_0^2 - (V_0 + \Delta V)} \frac{d^2 y}{dt^2} + y = 0$$

where parameter r_0 corresponds to the heart rate with complete absence vagus inhibition, V_0 to the normal pacemaker inhibition, and ΔV the changes pacemaker inhibition caused by respiration; y is the output of the pacemak and has a periodic solution. The maxima of y are considered to correspond the firing of the pacemaker.

(3) The pupillary reflex to light is mathematically described as

$$\frac{\mathfrak{D}}{\mathfrak{L}} = \frac{-b e^{-T_5 s}}{(1 + T_4 s)} + \Omega \frac{-a s e^{-T_3 s}}{(1 + T_1 s)(1 + T_2 s)}$$

where s is the Laplace operator
$\mathfrak{D}$ the Laplace transform of the pupil diameter
$\mathfrak{L}$ the Laplace transform of the light intensity
T_1, T_2, T_3, T_4, T_5 are time constants
a, b sensitivity constants.

Typical values for the time constants and other parameters are indicated in the listed references.

In the usual notation these equations are:

$$D + T_4 \frac{dD}{d(t + T_5)} + bL = 0$$

for the "proportional" response

$$D + (T_1 + T_2) \frac{dD}{d(t + T_3)} + T_1T_2 \frac{d^2D}{d(t + T_3)^2} + a\left[\frac{dL^+}{dt}\right] = 0$$

for the rate sensitive response

where D is the pupil diameter
L is the light intensity

and the + sign on the term in square brackets denotes that dL/dt can have only positive values.

Acknowledgment

The help of Michael Kohn, Frances Tanaka, and Kenneth Lifshitz in the preparation of this paper is gratefully acknowledged.

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Herbert H. Jasper (*Montreal Neurological Institute, McGill University, Montreal, Que., Canada*): It is a great pleasure to be able to contribute to this international monograph on higher nervous activity. For those of us who had the pleasure of taking part in the previous conference of this type, the Moscow Colloquium on Electroencephalography of Higher Nervous Activity, held in October 1958, the similarities and differences between the two programs come immediately to mind. If the present publication achieves even one half as much as was accomplished by the Moscow Colloquium, it should be considered a success indeed.

It is apparent from the papers in these pages that much has been accomplished during the past two years, both in Soviet and American laboratories working on essentially the same problems from different approaches and with somewhat different methods. It is interesting, as well, to see that our approaches in methods are not as different as they used to be. Monographs such as this serve to increase the areas of understanding and agreement in this difficult field of research. They also bring out important differences and serve to sharpen our points of view so that we may think more clearly about some of these most complicated problems.

The perfection of electrophysiological techniques capable of recording the electrical activity of local areas of the brain, and even the discharge patterns of single cells in the brain, throughout the conditioning process, is making it possible to test some of the hypotheses that have been proposed, by Pavlov and others, to explain brain mechanisms underlying complex behavior and learning.

The wealth of data, especially with unit analyses, that can be accumulated with these new methods, brings with it new problems of interpretation. It might be naively assumed that Pavlovian conceptions of local states of excitation, or the various forms of local or irradiating inhibition, might be directly tested by electrophysiological methods. However, when this is attempted, difficulties arise in the interpretation of the electrical activity of the brain in relation to processes of excitation and inhibition, and in relation to behavior.

For example, it was shown quite clearly in the Moscow Colloquium two years ago that one could not identify the desynchronized arousal pattern of the surface EEG with the excitatory states of Pavlov, nor was it safe to identify the desynchronized or slow-wave pattern in the EEG with Pavlovian inhibition. There was a very general correlation, as a rule, between the orienting or alerting response or state of the animal and desynchronization of the surface EEG and, of course, a general correlation between gross inhibitory states such as those associated with sleep, and the synchronized or slow-wave pattern in the surface EEG. Unit analysis, however, has even shown this general correlation to be more complicated than would be suspected. Important inhibitory processes can be shown to be taking place in the arrest of cell discharge during behavioral responses associated with a desynchronized EEG, while a regrouping of unit discharges, rather than a general inhibition, is associated commonly with the desynchronized or slow-wave sleep pattern of the EEG.

Anokhin has made a real contribution to this more refined analysis of the

electrical activity of the brain, as he describes it, to get behind the "mask" of gross synchronizing or desynchronizing effects upon cortical electrical activity. His application of microelectrodes and more refined analyses to the structuring of the brain stem reticular system is in line with many other studies that show this is not a homogeneous activating system. It is a very finely organized network of neurones, with differentiation for both inhibitory and excitatory functions and with differential chemical sensitivities and highly integrative patterning in their organization.

All of these studies, when microelectrodes are used carefully, indicate that any pattern of activation in the brain cannot be described adequately in terms of either excitation or inhibition, but both are combined always. One finds excitation occurring in one cell while inhibition occurs in adjacent cells not more than 50 to 100 μ distant. Microelectrode analyses of sensory systems, such as auditory, visual, or somatic, have all indicated that the activation of a sensory system is accompanied by just as much inhibition as excitation, in most instances, and that the two processes are finely patterned in an integrated manner, even in the retina. It would perhaps be better, therefore, to speak of specific and nonspecific *activation*, rather than either excitation or inhibition, to describe more accurately the nature of these neurophysiological processes.

This brings us to the question of what is to be considered specific and what is to be considered nonspecific. Anokhin has proposed to analyze specific and nonspecific afferents to the cortex by assuming that the surface-positive evoked potential represented an electrical sign of specific afferents while the surface-negative slower wave of longer latency could be interpreted as an evoked potential of nonspecific origin. In view of the fact that the positive-negative complex may arise from single shocks delivered to a specific thalamic nucleus, it may be hazardous to infer separate nonspecific pathways for the negative component of this evoked potential process. This is even more apparent when one considers Galambos's remarkable observations that a complete positive-negative evoked potential complex could be induced in the auditory cortex, even following bilateral section of the specific auditory pathways in the midbrain. This complex seems therefore to arise either from the specific system or from the so-called nonspecific system of projections to the cortex, depending on the level of anesthesia and other conditions.

It appears from many recent studies that the so-called extralimniscal sensory system passing up the core of the brain stem can no longer be considered necessarily an entire nonspecific system, but it must contain relatively specific components as well as relatively unspecific ones: excitatory and inhibitory mechanisms in a finely interwoven pattern of integrative organization, not adequately described as an activating or "arousal" system.

In order to illustrate some of the difficulties in identifying electrical activity or responses of the brain with definite aspects of behavior, I shall report briefly on the results obtained recently with Jerzy Majkowski, who has been working in my laboratories during the past year as a Fellow of the Rockefeller Foundation from Warsaw, Poland. We have been studying a defensive conditioned reflex in cats with implanted electrodes in the various parts of the brain, including the primary auditory cortex and the sensory-motor areas. We have used rhythmic clicks at frequencies between about 5 and 20 per second as the condi-

tioning stimulus. The unconditioned stimulus was a rhythmic electrical sho
to the forepaw synchronized at the same frequency as the clicks; in other wor
if we were conditioning to a click of 5/sec. the animal would receive a shock
5/sec. Responses to these shocks would be rhythmic movements during t
withdrawal of the limb.

During the first training period, trains of clicks alone without shock were a
ministered in 30 to 50 trials per day. Gradually the evoked potentials from t
auditory cortex diminished until, after about 150 to 200 trials, the avera
evoked potential amplitude would fall to less than one half of its original val

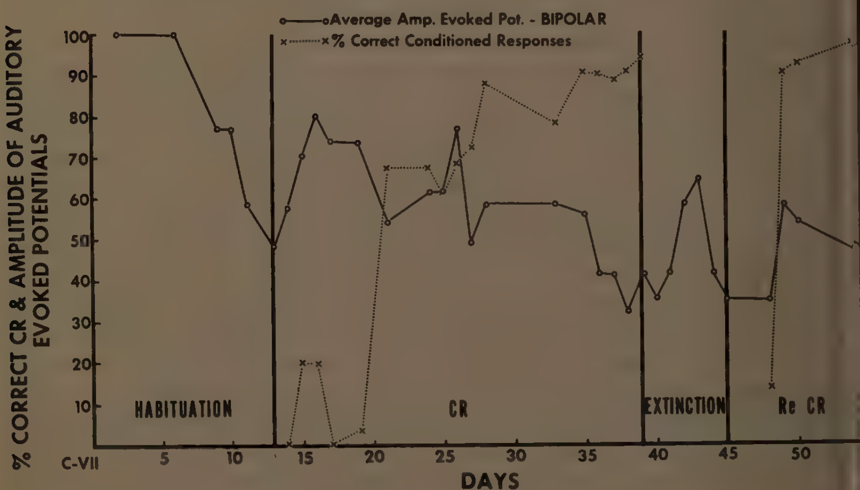

FIGURE 1. The curve of the "over-all" percentage amplitude of the evoked potentials r
corded with an ink-writing oscillograph from bipolar implanted electrodes (3 mm. apart)
the primary auditory cortex of the cat (*solid line*), plotted with the percentage of corre
conditioned avoidance responses to trains of 5/sec. clicks (CS). Each point on the evok
potential curve represents an average of about 400 potential amplitudes on a given day, r
duced to the percentage of the average amplitude in the initial control series. The curves a
based on a single cat studied daily for 55 days, and they are fairly representative of other a
mals in the series. See text for further description and discussion.

or sometimes less. This was true only if the conditions of the experiment we
rigidly maintained.

When conditioning was begun, combining rhythmic shocks with the clic
after a 3-sec. delay period, the evoked potentials did not suddenly return
their prehabituation level but gradually, about the second or third day, th
would approach the prehabituation level, although not above it. This recove
of evoked potentials during conditioning has been noted by some to represent
conditioning process. In our experiments, however, the evoked potentials r
covered before the animal was performing a significant number of condition
avoidance responses, so that the correlation between the return of evoked p
tentials and behavior was actually very poor.

As conditioning proceeded, and the animal began to learn to avoid succe

fully the shock with withdrawal of his paw to the click before the shock was administered, the evoked potentials actually began to decline in amplitude. When the percentage of correct conditioned responses reached levels of 90 to 95 per cent in successive daily series of trials, the evoked potentials declined further and reached a very low value, even below that obtained in the habituation series, or only about one quarter the prehabituation level. Thus the evoked potential seemed to be the lowest when the percentage of conditioned responses was at the highest level, after about 15 to 20 days of conditioning. These results are shown on the graph of FIGURE 1, the solid line being the percentage amplitude of auditory evoked potentials to the conditioning stimulus, while the dotted line represents the percentage of correct conditioned responses.

It is also of considerable interest to note the changes in auditory evoked potentials in this animal at the beginning of the extinction series when once again the clicks were presented without reinforcement. Initially the evoked potentials remained at a very low level, but they showed a very rapid rise and a fall again at the end of the extinction period. Finally, upon reconditioning after extinction, the evoked potentials showed, on the second day, another rise-to-fall again, as shown in FIGURE 1.

One cannot help drawing a parallel between these successive changes in evoked potential amplitudes during habituation conditioning and extinction and the curves of the blocking reactions shown by Doty. It is obvious that the relationship between the evoked potentials or the blocking reaction and the establishment of a conditioned response is complex. It would seem that the level of these types of response was more nearly related to an alerting reaction, not necessarily to conditioning as such.

The suspicion that these cortical evoked potentials were not necessarily essentially related to this type of conditioned response formation was confirmed when it was found that the very large excision of all auditory cortex bilaterally in these animals did not interfere with the establishment of this conditioned response. These results, together with the effects of pharmacological agents, will be reported by Majkowski.

JERZY MAJKOWSKI (*Montreal Neurological Institute, Montreal, Canada**): I propose to discuss one of the subjects raised by Anokhin in his very interesting paper, namely, psychopharmacology. I shall restrict myself to the action of adrenaline and chlorpromazine on the performance of conditioned responses and discrimination after removal of the auditory cortex and surrounding areas and after section of the brachium colliculi inferiores (BCI). These observations are based on certain aspects of work performed with H. H. Jasper in his laboratory in Montreal. The method of formation of the avoidance motor conditional reflex (AMCR) and discrimination was described by Jasper above.

After the establishment in cats of the AMCR and discrimination at the level of 90 to 100 per cent correct responses, surgical operations were performed. During the cats' postoperative training we observed in some of them two different types, roughly speaking, of conditional behavior. The first was the inhibitory type: the percentage of conditional reflexes was low and differentia-

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tion was high; the second was the excitatory type: the percentage of conditional reflexes was high but differentiation was very poor.

We tested the action of adrenaline in the first, the inhibitory group, and the action of chlorpromazine in the second, the excitatory group.

The Action of Adrenaline

After removal of the cortical auditory areas the AMCR and differentiation could be re-established without particular difficulty. However when we changed the meaning of the conditioned stimulus (CS) and the differential stimulus (DS)—when, in other words, we changed the CS to a DS and the DS to a CS—we were not able to achieve as high a level of positive conditioned responses (CR) as before. The percentage varied from day to day between 60 and 80 per cent. In addition, in order to reach such a response level it was necessary to increase the intervals between trials. We observed also that the conditioned responses were delayed, and at this time discrimination was high. It was obvious that the cat in question was inhibited.

For a 7-day period this cat received adrenaline intravenously just before the experiment in doses of 15 γ/kg. of weight or, intramuscularly, 1 hour before the experiment in doses of 45 to 70 γ/kg. of weight.

The effect of adrenaline may be summarized as follows: (1) the percentage of positive AMCRs was higher (93 to 96 per cent) and was constant during successive days of injection; (2) the intervals between trials could be shorter; and (3) the delay of the AMCR was also shorter. When adrenaline was withdrawn, the level of the AMCR dropped to 65 per cent, but after repeated injections it rose again to 93 per cent.

It is important to emphasize that there was no decrease in the level of discrimination after injections of adrenaline.

Hence we concluded that adrenaline increases the percentage of conditional reflexes in this case, following surgery that resulted in the predominance of inhibition.

The Action of Chlorpromazine

We tested the effects of chlorpromazine on several cats displaying the second type of behavior: that in which the percentage of conditional reflexes was high but in which there is very poor or no differentiation.

On the basis of 18 experiments in three cats, in which more than 1000 presentations of CS and DS were made, we came to the conclusion that there does exist an optimal dose of chlorpromazine with which we were able to obtain a very high level of discrimination—about 90 per cent—with a very small variation in the level of conditional reflexes.

The chlorpromazine doses we administered varied from 15 to 100 γ/kg. of the cat's body weight; the optimal dose varied from 15 to 30 γ/kg. It is important to note that there is also an optimal time for the best responses following the injection of the drug that depends largely on the size of the dose.

When the dose of chlorpromazine was too large the conditional reflexes decreased. In such cases, of course, we cannot speak of the improvement of differentiation.

Thus it appears that in the excitatory type of behavior, in which differentiation is poor, there is a possibility of improvement by increasing the level of inhibition in the reticular formation of the brain stem.

In conclusion, it seems that the administration of adrenaline or chlorpromazine permits the increase of percentages of AMCR and differentiation through manipulation of the balance of excitation and inhibition in the brain stem's reticular formation.

Fred A. Mettler (*College of Physicians and Surgeons, Columbia University, New York, N. Y.*): Magoun has referred to a recent marriage between electrophysiology and conditioned techniques. This marriage is not new, it is merely sterile.

At the present time, when issue is finally threatened, it behooves us to exercise a measure of prenatal care in order to assure that the result will not be a monster. The important point is, or course, not whether electroneurophysiological phenomena can be found that occur in the course of modified neural activity, but rather what correlations can be established between electrophysiological events and psychologically significant physiological events. It is not enough to allocate electrophysiological properties to large areas of the brain stem, such as the tegmentum, since this may turn out to be merely a reaffirmation of general properties common to the neural system in general. Nor is it enough to define specific features of electrophysiological exercises since, as Grundfest and Miller point out, such specific functions may be irrelevant to the learning process.

Anokhin has directed his attention to this essential problem of correlation and he has pointed out that the core systems are not, in fact, diffuse; he has cited the researches of Jasper and Purpura in this connection.

In addition, Galambos has shown us that the nonspecific systems are not necessarily slow systems.

Anokhin has, I think, successfully isolated the significant from the insignificant material in the maze of constantly confusing and apparently contradictory material available to us, and he has pointed to the really important parts of it.

In essence, both specific and nonspecific systems play important roles in the development of learning, but fully differentiated learning requires the integrity of specific systems. Knowledge of these circumstances has been available to us for a long time.

The fact that subcortical changes occur in learning does not place the locus of learning in the subcortex. More than a quarter of a century ago, Poltyrev and Zeliony in the Soviet Union, and Zeliony, even earlier in France, demonstrated that conditioning is possible in decorticated animals.

As Miller pointed out in his comments, this subject was extensively pursued in the United States by Culler, Finch, and Brogden, and by Girden; the latter is now at Brooklyn College, in New York, N. Y. These experiments indicated that animals totally deprived of cortex, and thus of both the Pavlovian analyzer and effector systems, were still conditionable.

Anokhin believes that the specific systems provide the initial event in both subcortical and cortical activity. The fact that generalized desynchronization

occurs should not, he points out, be allowed to obscure the possibility that highly specific and fully organized differential processes occur in the cortex.

In deciding what correlations between electrophysiology and psychologically significant physiological events are important, the profitable limiting factor would seem to be the demonstrable microscopic anatomy of the nervous system.

ANOKHIN: I thank the discussants for raising significant points, not only in regard to my paper but also, in general, as regards the problem of correlation between cortex and subcortical levels. This problem, following the discovery of physiological peculiarities of the reticular formation, is of extreme importance. The brain is really the mechanism of our psychological activity, but in this region we have very many difficulties, naturally: difficulties in taking first steps and in determining different lines of investigation. All we investigators have one purpose: the study of the brain and its function; but we differ in our lives and traditions. In the present epoch we must inevitably elaborate one language for all physiologists that is applicable in different areas. One such approach is electrophysiology, a region that has its own language, its own criteria. Another approach is that of morphology and the morphological study of connections between different elements of the brain; the criteria and manner of thinking in this field also are unique.

We Soviet physiologists consider the basic direction of study to be neurophysiology, not psychophysiology; we believe that higher nervous activity is primarily neurophysiological in nature, with very complex indicators of activity. This approach also elaborates its own methods, its own manner of thinking; from this basic starting position, we join with other workers using different approaches to reach the same goal: the discovery and explanation of the mechanisms of conditioned reflexes. It is natural that we have very often sought coordination of the various approaches and methods.

Therefore, I was especially pleased to receive a letter from Corson of Yale University, New Haven, Conn., who urged that my book on this subject be translated into English. I should be very glad to make Soviet concepts of internal inhibition, cortical inhibition, and the general mechanisms of the conditioned reflex more easily available to our American friends.

Doty shows elsewhere in these papers that subcortical structure is very significant for elaboration of the conditioned reflex. That is true, and it is the first tenet of Pavlov's school that each subcortical nucleus has its own particular concrete mechanism. We knew last year of Doty's great interest in this area; he showed then that *energetic action or activation* in terms of Magoun's system, from the brain stem to the cortical levels, is a very significant function that facilitates connections on different layers of the cortex, for the cortical point is excited *into* an anesthetic state. It is known that stimulation of the sciatic nerve gives a very good demonstrable evoked potential. When the test animals sleep, there is still the problem of specific impulse in the cortex which is only half the problem. There must be nonspecific activation from the subcortex; when this activation is too energetic for a very fine cortical specific point—I emphasize that this is only my opinion—only in these conditions may the irradiation of specific impulses, the selective stimulation, help these impulses from the subcortical areas. There is organic connection only to activities in integrated coordination in action at the cortical level.

Doty's very interesting facts will, most probably, affect our work in our own laboratories.

Jasper, who is a specialist in this region, naturally desires to be careful in explaining the negative phase of the primary surface potential, and we are also cautious in discussing this problem. I especially emphasize that in this connection we elucidate two problems. The first is the problem of the positive and negative phase of which the evoked potentials are physiologically different; the second proposition hypothesizes that in the ontogenetic stage before birth and during first and second days after birth a pleximorphic layer of the cortex is matured, but layers 3 and 4 and especially the symmetrical connections on this level are not matured. At this moment there is a negative phase of the evoked potential and a correlation of the morphological structures in these periods of development.

On this basis, we ought to have theoretical study, and naturally we are working in this direction more and more.

At present new experimental work is being done in this area. For instance, the evoked potential in the newborn rabbit and the genetic peak in different layers of the cortex is being studied by Brogden, and we shall hear more in the future in this connection.

Majkowski raised a very interesting point that has been under investigation in my laboratory for the last 10 years. This point may be defined as the correlations in the adrenergic substrate of the reticular formation between chlorpromazine and adrenaline, a very significant problem. We performed a neat experiment that I think may be interesting to Jasper and his co-workers. A dog in one test chamber elaborated the defensive reaction; in another chamber, it showed only the feed reaction. On the same conditioned stimulus, but in two different chambers in different parts of the laboratory, this dog—a very normal animal, such as we prefer in Pavlovian laboratories—on this same stimulus, with feeding conditions similar, gave a jerking reaction. I feel that this merits consideration, but I do not know why. This is a very interesting reaction, and I am glad that Jasper's experiments go in this direction; I feel that this region is very promising for neurophysiology and neuropharmacology.

I absolutely agree with Mettler. Since 1932 in my laboratory, I have continuously operated a morphological study and also a number of special ontogenetic investigations. My co-workers and I have correlated the physiological and the morphological aspects, because, especially in ontogenetic development, every hour, every day, and every week, new light has been thrown on different substrates. Without correlation between the morphological and physiological evidence I think it would be impossible to solve problems of cortical and subcortical relations and, particularly, to offer explanations of evoked potentials in newborn rats, of genetics, and of the interesting question of maturation in ontogenetic study. We are now at a very interesting phase that shows the different stages of development reached on several levels of the study of morphology.

In the course of studying the correlation of the effects of chlorpromazine and adrenaline, we found a very radical change in structure. Early in the experiments, desynchronization appeared, but chlorpromazine in this stage

did not act upon it. By the end of five days of continuous study, however measurable desynchronization was noted, but chlorpromazine in this stag blocked it.

HAROLD HIMWICH (*Galesburg State Research Hospital, Galesburg, Ill.*): Th excellent analysis that Anokhin[1] has made, showing the relationships of bio logically negative reactions to the alert electroencephalogram and biologicall positive reactions to the synchronized electroencephalogram, is most interesting especially because aminazine or, as Americans call it, chlorpromazine, is able t prevent both aspects of the defensive or nociceptive action, namely, that o behavior and of the electroencephalogram. That courting behavior an copulation in rabbits is followed by typical changes in the EEG has been show by Kamakawi and Sawyer (Sawyer[2]). Immediately after mating these worker observed several minutes of sleeplike record which, in turn, is followed by a

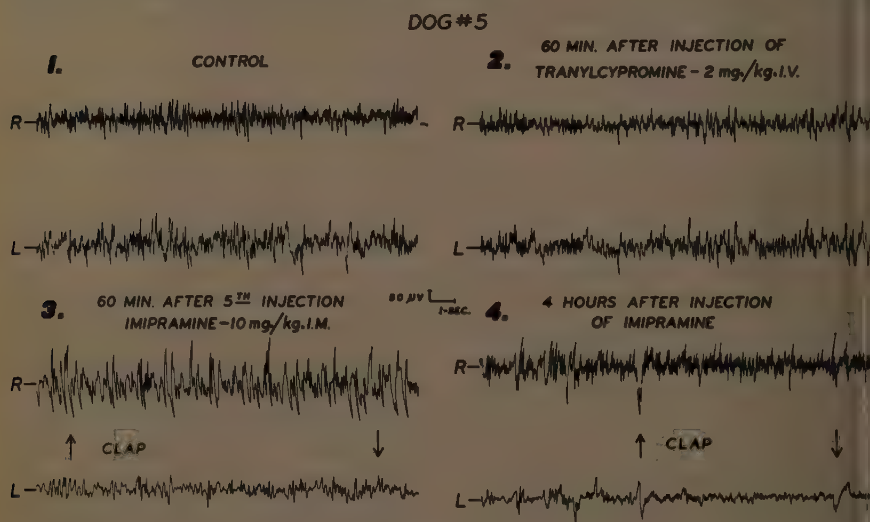

FIGURE 1.

unusual arousal pattern. This pattern has been termed pseudo-arousal b these workers because, despite an extreme degree of EEG arousal, the rab bit remains quiescent. Thus, following sexual intercourse, a behavioral seda tionlike condition is associated with EEG arousal.

Recently Williamina A. Himwich *et al.*[3] have been able to study the EE pattern before, during, and after simulated sexual intercourse induced by drugs FIGURE 1 reveals the various control conditions, all obtained on a male dog Number 5. The tracings grouped under **1** reveal the EEG of an unanesthetize unrestrained dog with silver ball electrodes implanted on the dura of the moto cortex. Under **2**, 60 min. after I.V. injection of tranylcypromine,* 2 mg./kg. there is very little change in the EEG and behavior, although the animal wa slightly more alert. Sixty minutes after the fifth daily injection (**3**) of imipra mine,† 10 mg./kg., the animal is drowsy, as is his EEG. He fails to alert i response to handclap.

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† Tofranil, Geigy Pharmaceuticals Division, Geigy Chemical Corporation, Ardsley, N. Y

Four hours after the injection of imipramine (**4**) both the EEG and the animal show evidence of sleepiness, although there is some slight evidence of alerting in response to the sound of a handclap.

FIGURE 2 was obtained on the same dog one month later. The top tracings reveal partial alerting of the EEG 24 hours after the fourth daily dose of imipramine (I.M. 10 mg./kg.). The animal does not show much change behaviorally. The second group of tracings, made after the fifth dose of imipramine, was followed immediately by one of tranylcypromine, resulting in a drowsy pattern that could not be changed by handclap. The lower left tracing exhibits the EEG taken 2 hours after the injection of imipramine and tranylcypromine, during a period in which there were repeated orgasms consisting of sexual movements simulating copulation. The electroencephalogram showed alertness throughout this sexual activity, and this alerting occurred at a time when the animal was not responsive to external stimuli. Finally, the lower right group shows that after 1 to 2 hours of repeated orgasms the animal goes back to sleep and cannot be aroused by handclap.

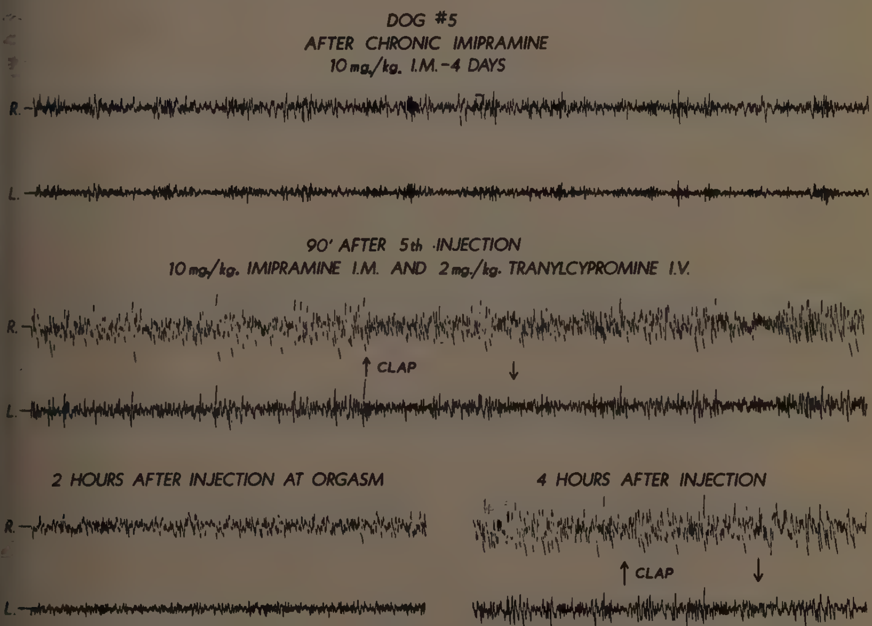

FIGURE 2.

It is of interest that 4 hours after injection of tranylcypromine and imipramine a biologically positive reaction is associated with an alert EEG during orgasms in a dog. As a result of the combined administration of imipramine and tranylcypromine, the EEG has the usual characteristics of sleep except during sexual activity. It is not surprising that a biologically positive reaction necessary for the survival of the species is associated with an alert EEG, in view of the fact that total bodily resources must be mobilized during sexual intercourse.

Summary

A biologically positive activity that is, however, associated with the mobiliza tion of the bodily resources, is accompanied by an alert EEG.

By means of drugs, imipramine combined with tranylcypromine, it has been possible to reproduce the behavioral effects of mating activity in dogs and to study the associated EEG pattern.

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PAVLOV, THE PSYCHIATRIST OF THE FUTURE

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I propose first to speak of Pavlov. This extremely gifted experimental physiologist, a human being both vehement and fallible, has been to me a life-long inspiration in my own scientific endeavors and in those of my co-workers and friends.

On an August day in 1926, W. Horsley Gantt and I met for the first time in Leningrad. It was not by accident that we met in Pavlov's laboratory, for both of us were pursuing the same goal: namely, a first-hand practical knowledge of Pavlov's method of the conditioned reflex. We believed then and believe now that the persevering use of this powerful and exact method in the field of experimental medicine can disclose the biological basis of many fundamental problems concerning mental health and disease.

In 1923 G. V. Anrep, a former assistant to Pavlov, lectured at Cornell University on the conditioned reflex and, in concluding his lecture, described the onset of experimental neurosis in one of Pavlov's dogs. While in Ithaca, he advised me on the construction of a small conditioning laboratory in which to test the effect of thyroidectomy in sheep and goats on their conditioned reflexes. With Anrep's description of experimental neurosis in mind, I was able to recognize in 1927 the manifestations of this chronic abnormal behavioral pattern in one of our normal sheep when it was subjected to a regimen of arduous conditioning.

We thereafter neglected the thyroid problem and concentrated more and more on the systematic analysis of Pavlovian conditioning as a stressful procedure leading to patterns of abnormal behavior in the sheep, goat, pig, and dog. In this comparative study, we discovered that Pavlov's phenomena of higher nervous activity are observed in each of these mammalian species in detail. Moreover, his powerful method of the conditioned reflex provides us with the *vade mecum* to experimental psychiatry.

The year of 1929 marked a turning point in the history of our laboratory. Through the good offices of Gantt, I had earlier met in Leningrad our distinguished colleague P. S. Kupalov who, as a traveling fellow, worked in our laboratory in Ithaca during the summer of 1929. It was his broad and unbiased appraisal of the details of Pavlov's conditioned-reflex investigations then in progress that gave us confidence in the basic importance for medicine of this field of research, then almost unknown to investigators in the United States.

In August of that year, the International Physiological Congress met in Boston, Mass.; Gantt, terminating his six years of work in Pavlov's laboratory, came to Boston, where he, Pavlov, Kupalov, and myself were able to confer at length. Adolf Meyer, meanwhile, had enabled Gantt to establish a conditioning laboratory, the present Pavlovian laboratory at the Phipps Clinic of the Johns Hopkins Hospital, Baltimore, Md.

In May 1955, we celebrated the 25th anniversary of the Pavlovian laboratory and, at Gantt's instigation, organized the Pavlovian Society for the Advancement of Objective Psychiatry.

Pavlov was in Finland when I visited his laboratory in 1926. My first meeting with him in Boston was both frustrating and amusing. I saw him seated on a bench on the Harvard Medical School campus. I approached and introduced myself. In the ensuing conversation, I was limited to my high school German. He spoke international German. "By international German," he once told a colleague, "I mean that all foreigners understand me, but no German does."

At subsequent meetings, Kupalov served as my interpreter, as he did in an hour's conference with Pavlov about our work during my visit to his laboratory in the spring of 1934. During our conversation, he asked me how we found working with pigs. I said it was difficult; in fact, it took three of us to hoist a screaming 100-lb. pig onto a table and into the Pavlov restraining frame.

On the next day, at his Wednesday afternoon seminar, he discussed our work in Ithaca and recounted his own experiences with pigs. I remember well his remarks. He said, "My first experience with pigs was not as a physiologist, but as a small boy. When pigs got into our garden, we chased them. Suddenly one day, a pig fell down, screaming in an hysterical fit, and we could have killed it if we wished. Later, as a physiologist, I collected gastric juice from dogs for therapeutic use. Patients refused it because it came from dogs, so I decided to use pigs. Everybody eats pigs; so, why be against pigs? We established a gastric fistula in a pig and placed it on the table in the frame. It screamed at the top of its lungs and all work in the laboratory was impossible. All attempts to sooth it were in vain. Then it went into an hysterical fit. It was constipated; there was no gastric juice, and the gastric mucosa became hard as shoe leather. Further work with it was impossible and we gave it to the attendants as an Easter present."

At Cornell, we persevered where Pavlov changed to an easier animal, the dog. George Sutherland, A. U. Moore, and Frederick Marcuse succeeded in conditioning four pigs in conventional salivary methods used by Pavlov. We found that this was possible by taking the young pig on leash shortly after weaning; the animal soon became accustomed to this daily exercise and could be lured into the laboratory and then into the Pavlov frame.

The Pavlov pig is a virtuoso at salivary secretion. Munching one dog biscuit, he will secrete parotid saliva in squirts for as long as 20 minutes.

My colleague and friend, Kupalov, is a master experimental physiologist. I challenge him to attempt to inhibit the unconditioned salivary reflex of the pig, as he reports in these pages that he has done in the dog. I'm quite sure that he would succeed, however.

The experimental neurosis in the pig is a matter of great interest. The neurotic pig is a dangerous animal. With the onset of the neurosis, it slides into a paranoid gulch, and its sole aim in life seems to be to attack the experimenter by fair means or foul.

George Sutherland left his neurotic sow, Tiny, then 400 lb. in weight, to work for a year in Massachusetts General Hospital in Boston. When he re-

turned after this year she, by friendly overtures, lured him into a fence corner and attacked him so viciously that he required medical attention.

During my visit to Pavlov's laboratory in 1934, I remember with pleasure a dinner at which I told his colleagues that I regarded Pavlov's laboratory as my physiological home. All of Pavlov's co-workers that I have met have been ambassadors of international scientific good will. I wish in particular to salute, in memoriam, my dear friend L. A. Andreyev, who was such an ambassador during the years of 1933 and 1934 while he was guest investigator with the late Boris Babkin at McGill University, Montreal, P.Q., Canada.

A final word of appraisal and appreciation of Pavlov's character and of his basic contribution to human thinking and feeling: Pavlov was an unswerving idealist and truth seeker. His whole career was dominated by his tenacity. His singleness of purpose made him continually ask "Why?" throughout his long life as a daily experimenter. For most of Pavlov's professional life, the physiologist's tools, both electrical and chemical, were too few and too blunt. Consequently, the brain operated in secret within its skull. However, such was the vividness and prevision of his scientific imagination that he wrote in 1913 as follows:

"If we could look through the skull into the brain of a consciously thinking person and if the place of optimal excitability were luminous, then we should see playing over the cerebral surface a bright spot with fantastic waving borders, constantly fluctuating in size and form, surrounded by darkness, more or less deep, covering the rest of the hemispheres."

We can imagine Pavlov's enthusiasm were he reviewing this publication, with its accounts of the physiologists' recent advances in disclosing the intricate operations of the living brain.

THE EFFECTS OF PHARMACOLOGICAL AGENTS ON CONDITIONED AND UNCONDITIONED REFLEXES

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The neuron theory and the theory of reflexes created the conditions that have made it possible to study the effects of pharmacological agents on the nervous system. Physiological analysis shows that changes arising in nervous activity under the influence of general anesthetics, analgesics, neuroplegics, ganglioplegics, and many other agents depend primarily on changes in synaptic transmission of nerve impulses.

As we all know, every manifestation of nervous activity is associated with interneuronal transmission of excitation. As far back as the 1860s I. M. Sechenov[1] pointed out the great importance of interneuronal contacts in the activity of the nervous system. It was his view that "except in terms of intercellular connections it would, in fact, be impossible to explain the mode of production of even the most elementary reflex."[1]

The most recent investigations fully confirm the important role of interneuronal synapses in central nervous system activity. Without interneuronal synapses, it is impossible to conceive of the principle of permanent (constant) and temporary connections—that is, the formation of unconditioned and conditioned reflexes—that lies at the root of all outward manifestations of nervous activity.

The hypothesis that the interneuronal synapses are the site of action of many neurotropic agents was advanced long ago in consequence of certain logical presuppositions. Even in 1866, before the neuron theory appeared, A. Ya. Danilevskii, speaking about the sites of action of general anesthetics in the central nervous system, expressed the opinion that diethyl ether affects "the cells' communication system."[2] Since that time, this remarkable guess has been confirmed by the investigations of many authors. By a variety of methods, convincing proof has been obtained that the interneuronal synapses are the sites of action of diethyl ether and other general anesthetics in the central nervous system.

In recent years, my colleagues and I[3-9,11] have succeeded in turning up a number of new facts in support of the view that changes in nervous activity under the influence of many pharmacological agents depend on changes in interneuronal transmission of excitation.

As one characteristic of the transmission of excitation from neuron to neuron the central reflex time may be used. Numerous investigations carried out in our laboratory on the time required for synaptic transmission have shown that drugs having a general-anesthetic type of action basically work by impeding interneuronal transmission, in contrast to substances that stimulate nervous activity and work by facilitating transmission. At the same time, these substances have different effects on synaptic transmission in different centers, which explains the special characteristics of each one's action.

By determining the central reflex time for reflexes with centers at different

levels, we have demonstrated sizable differences in the sensitivity of these centers to general anesthetics. It has been shown that the sensitivities of different nervous centers to general anesthetics may differ by a large factor. For example, diethyl ether inhibits the hind-limb flexor reflex at a concentration only $\frac{1}{18}$ of that required to inhibit the eyelid closure reflex, and only $\frac{1}{22}$ of that required to inhibit the respiratory reflex.

According to A. V. Valdman's data,[12,13] the patellar reflex, a proprioceptive bineuronal reflex, is not inhibited by general anesthetics (for example urethan and chloral hydrate), even in anesthetic doses; and analeptics (such as caffeine, pentylenetetrazol, strychnine, and nikethamide) do not enhance this reflex. Anticholinesterases (physostigmine and neostigmine) markedly increase the amplitude of the patellar reflex, although cholinergic agents (acetylcholine and carbachol) produce only an insignificant increase in amplitude. The patellar reflex is very responsive to nicotine, the principal representative of the class of ganglioplegic substances, which enhances this reflex in small doses and inhibits it in large doses.

According to Valdman's observations, when the patellar reflex is completely abolished by nicotine, the crossed-extensor reflex is retained; when the crossed-extensor reflex is completely abolished by general anesthetics, the patellar reflex is unchanged. In this case, we must bear in mind that the crossed-extensor reflex and the patellar reflex have common afferent pathways.

General anesthetics, analeptics, and cholinergic agents have more pronounced effects on the crossed-extensor reflex than on the flexor reflex. The flexor reflex, too, has afferent pathways in common with the crossed-extensor reflex.

Valdman[14,15] has also been able to show differences in the effects of general anesthetics and cholinergic agents on reflexes that have common efferent but different afferent pathways. This was illustrated by the differential action of these substances on the eyelid closure reflex in response to photic stimulation of the retina, tactile stimulation of the cornea, and electrical stimulation of the conjunctiva: that is, by stimulation of different receptor zones. These experiments established that general anesthetics inhibit the eyelid reflex to light more readily than the eyelid reflex to tactile or electrical stimulation, and cholinergic agents inhibit the reflex to light and tactile stimulation more readily than the reflex to electrical stimulation.

Various autonomic reflexes are distinguished by a high degree of resistance to pharmacological agents. Thus, according to N. V. Kaverina's investigations,[16-19] general anesthetics (barbital, amobarbital, thiopental, and urethan) have only a slight effect on the reflex circulatory changes that accompany stimulation of receptors in the colon, urinary bladder, and carotid sinus. General anesthetics inhibit these reflexes only when administered in doses that produce a marked drop in blood pressure. Procaine, thiphen,* and hypertonic glucose solutions are more effective in this respect, the first two of these having different effects on reflexes from different receptor zones: they inhibit reflexes from the colon and urinary bladder more readily than those from the carotid sinus.

* Not to be confused with another antispasmodic of the same name. This drug is the thioester analogue of 2-diethylaminoethyl diphenylacetate. (Translator.)

The circulatory reflexes that occur in response to stimulation of organs of the thoracic cavity are characterized by still greater resistance to pharmacological agents. As A. N. Ivanova[20] has found in our laboratory, in experiments with electrical, mechanical, thermal, and chemical stimulation of the parietal and visceral pleura, lung tissue, and the pulmonary hilar region, the effects of various pharmacological agents on reflex changes in the circulation are displayed in very distinctive ways. Thus substances having a general-anesthetic type of action (ethyl alcohol, diethyl ether, urethan, barbital, hexobarbital, and thiopental) completely suppress only the pressor reflexes from the parietal pleura, while they inhibit the depressor reflexes from the hilar region to a lesser extent. Incidentally, these reflexes are most pronounced following electrical and mechanical stimulation of the reflexogenic zones mentioned, and are very weak following thermal or chemical stimulation. Stimulation of the visceral pleura or the lung tissue proper is not accompanied by perceptible changes in the circulation. As regards the differences in the effect of general anesthetics on pressor and depressor reflexes, this is due to the particular features of the innervation of the parietal pleura and the hilar region. The former is innervated by intercostal nerves, and the latter by fibers that join the vagus nerves. Therefore, the centers of the corresponding reflex arcs are located at different levels of the central nervous system: that is, at the levels of the spinal cord and the medulla, respectively. Moreover, as mentioned above, the sensitivities of the central components of reflex arcs located at different levels of the central nervous system vary over a wide range.

Reflex reactions of the coronary vessels to stimulation of somatic nerves and the carotid sinus are highly resistant to analgesic agents (morphine, dihydrohydroxycodeinone, promedol, and methadone), as Kaverina's experiments have shown.

In exactly the same way, analgesics (see above) and neuroplegics (chlorpromazine and mepazine) are relatively ineffective against coronary chemoreflexes, to judge from the observations of I. N. Pidevich.[21]

The question of the effects of pharmacological agents on the transmission of excitation within the central nervous system following stimulation of afferent nerves is intimately connected with the question of the effects of these substances on the transmission of excitation from intracentral neurons: particularly from descending motor neurons, including those in the corticospinal (pyramidal) tracts. It was observed long ago that during general anesthesia, electrical stimulation of the motor cortex is accompanied by movement of the extremities; it follows that in such cases transmission of impulses from the pyramidal tracts to the spinal cord cells still takes place.

By measuring the latent period of the motor response to stimulation of the pyramidal tracts, we have found that general anesthetics (for example chloral hydrate, urethan, and barbital) have an effect on impulse transmission to the motor units of the spinal cord in smaller doses than those required to produce an effect when afferent pathways are stimulated.

The synapses between axons of the pyramidal tracts and the spinal cells are therefore more sensitive to anesthetics than are the synapses between spinal cord cells and the axons of afferent nerves. This can be explained on the basis

of phylogenetic data. Since it is generally true that those elements of the nervous system that developed later and are, consequently, the most highly differentiated, are more sensitive to injurious agents (specifically, to general anesthetics), the synapses of the pyramidal tracts (which are phylogenetically later formations than afferent nerve synapses) are thus more sensitive to general anesthetics.

N. A. Kruglov, who has studied the effects of chlorpromazine and mepazine on the ipsilateral hind-limb flexor reflex and the contralateral hind-limb extensor reflex in spinal and decerebrate cats, has shown that these neuroplegic agents, while they have no perceptible effect on these reflex processes in spinal cats, readily inhibit the contralateral extensor reflex in decerebrate animals. In addition to this, it is well known that the contralateral extensor reflex has a distinctly tonic character and involves the participation of tonic centers in the midbrain: that is, excitation travels not only through the particular segment of the spinal cord but also through the midbrain. In corresponding fashion, action potentials in the quadriceps femoris muscle following stimulation of the contralateral peroneal nerve consist of two components. The first small discharge passes along a short pathway through the spinal cord segment and has a short latent period (10 to 15 msec.). The second discharge, which is much larger, passes through the brain stem, as demonstrated by the absence of this component in spinal animals and by its longer latent period. Neuroplegic substances thus have no effect on the conduction of excitation in spinal mono- and polysynaptic reflex arcs, but they impede conduction of excitation in tonic centers of the brain stem. In other words, these substances do not affect the synaptic transmission of impulses in the segmental apparatus of the spinal cord, but distinctly alter the transmission of excitation in the region of the reticular formation of the brain stem.

Kruglov has very convincingly demonstrated an effect of morphine and other analgesics on interneurons. By experiments involving separate stimulation of the peroneal and tibial nerves under the influence of morphine, he showed that when the semitendinosus muscle relaxes as a result of prolonged stimulation of the peroneal nerve, stimulation of the tibial nerve is accompanied by a contraction of the semitendinosus muscle. In this case, therefore, the diminution of the flexor reflex results from inhibition, not of motor neurons, but of interneurons. It follows that analgesics have their effect on interneurons rather than on motor neurons.

Investigations carried out in our laboratory on the effect of general anesthetics on the transmission of central impulses to internal organs have shown that these substances are relatively inactive in this connection. Specifically, studies made by M. K. Sozina and myself[10] on the effect of general anesthetics on the transmission of central impulses to the circulatory organs have shown that in this respect the effect of general anesthetics is relatively slight. For example, chloral hydrate and barbital have only a small effect on the blood pressure changes that follow stimulation of the brain, even when administered in anesthetic doses. Similarly, they have an insignificant effect on changes in the renal blood flow following stimulation of the brain. These facts indicate that it is difficult in the extreme to abolish the transmission of central impulses

to the internal organs by using general anesthetics. To eliminate this type of transmission one must use other agents. Among a large number of substances that we have tested in this connection procaine was especially active.

On the basis of studies by numerous authors we may regard it as proved that different afferent systems show different sensitivities to pharmacological agents. In particular, it has been found that general anesthetics readily inhibit the transmission of nerve impulses along nonspecific afferent pathways, but far less readily along specific pathways. General anesthetics therefore largely abolish the activating effect of the reticular formation on the electrical activity of the cerebral cortex.

According to L. N. Sinitsin's data,[24] analgesic agents inhibit or completely suppress the conduction of afferent impulses to the thalamocortical association system, and inhibit the conduction of excitation to the ascending reticular system of the diencephalon and mesencephalon. At the same time, these substances do not disturb the conduction of excitation in the classical sensory tracts, and in large doses they increase primary responses in the sensory cortex.

The method of conditioned reflexes, introduced into physiology by I. P. Pavlov,[25] has opened up vast possibilities for studying the effects of pharmacological agents on the higher divisions of the central nervous system. Many drugs have been investigated in this manner, including ethyl alcohol and other general anesthetics, somnifacients, bromides, analgesics, and substances that stimulate nervous activity.

There is no question that the general patterns of the actions of particular pharmacological agents are the same, in their broad outlines, for the various divisions of the central nervous system; the differences are only of a quantitative nature, and depend on the different sensitivities of synaptic formations and on the complexity of the organization of individual nervous structures.

Pavlov himself pointed out the great similarity of the general principles of cerebral cortical activity and the activity of the segmental apparatus. Concerning this he wrote: "One cannot help seeing many, many points where facts that we have uncovered in studying the cerebral hemispheres coincide with facts about the physiology of the spinal cord, which shows the natural unity of the underlying relationships in the two areas."[25]

Pavlov believed[25] that his studies of cerebral cortical functions were analogous in character to those of Charles Sherrington on the spinal cord.

An analysis of the effects of various pharmacological agents on the higher divisions of the central nervous system, especially the cerebral cortex, allows us to state that substances having a depressant type of action inhibit the formation of conditioned connections, and those with stimulating effects facilitate the formation of conditioned connections. This should explain the effect of these agents on various manifestations of nervous activity, particularly processes of inhibition and irradiation.

We can therefore take it to be an established fact that the effects of many pharmacologic agents on conditioned and unconditioned reflexes are determined by their effects on synaptic transmission.

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INHIBITION AS A DETERMINANT OF SYNAPTIC AND BEHAVIORAL PATTERNS

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This is an integrated account and interpretation of work whose various parts have been done in collaboration respectively with E. Ross Hart, Oakley S. Ray, and Thomas M. Gilfoil.

The gamut of observable biological changes is the result and an expression of the two degrees of freedom possible to cell function in general and to neuronal function in particular, the increase and decrease that we recognize as excitation and inhibiton. The richness of patterns possible, therefore, and their consequences, must be interpretable in such terms.

The translation from functional units to behavioral patterns is an essential and ultimate requirement in real understanding of central nervous system activity. The use of drugs as tools has greatly aided in such analysis of function; in fact, it is the union of neuropharmacology and psychology that has created the new psychopharmacology.

The vulnerability of synapses to many chemical influences has made a pharmacological approach particularly significant. This is true in large part, because the vulnerability to drugs appears to be based on the rational premise of a chemical similarity of certain of them to cerebral neurohumors[1] whose equilibrium with antagonist neurohumors is a critical aspect of the synaptic chemical environment.

Recording the evoked potentials from the terminal cortical synapses of the transcallosal pathway joining symmetrical points in the association optic cortices of the lightly anesthetized (or curarized) cat has given us a means of studying a readily quantifiable functional "unit,"[2] which is sufficiently simple and sufficiently representative of cerebral synapses in general[1] to serve, so to speak, as a building block for patterns.

We have readily demonstrated in this way, through the use of close-arterial (intracarotid) injection and by the *in situ* accumulation of natural chemicals, that cerebral synapses are subject to the influence of and are controlled by excitatory neurohumors such as acetylcholine[2] (FIGURE 1) by inhibitory neurohumors such as serotonin,[3] adrenaline, and noradrenaline[2] (FIGURE 2), by natural synaptic inhibitors such as histamine[4] (FIGURE 3), and by gamma-aminobutyric acid (GABA)[5] (FIGURE 4), whose role in normal synaptic function is not yet clear. It is furthermore evident that these neurohumoral excitatory and inhibitory influences exist in a delicate equilibrium (FIGURE 5) which can be upset or distorted by changes in the metabolism of the neurohumors or by exposing the synapses to inhibitors such as amphetamine and the exogenous psychotogens, lysergic acid diethylamide (LSD-25), mescaline, bufotenine (FIGURE 6) and Kava extract.[7] All of these exogenous cerebral inhibitors are chemically more or less closely related to the natural cerebral inhibitors, including the inhibitory neurohumors.

The direct and more obvious effect of inhibition is reduced activity, but the

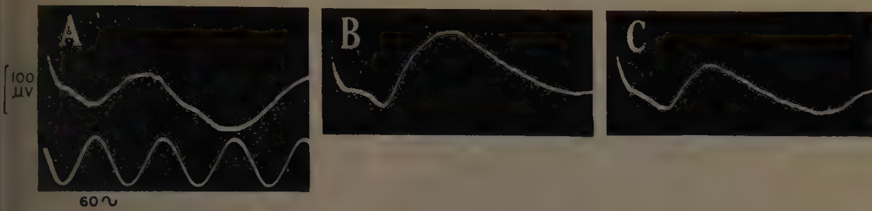


FIGURE 1. Cerebral synaptic action of acetylcholine in an intercortical (transcallosal) system. The potentials were evoked in the optic cortex by electrical stimulation of the symmetrical point in the contralateral cortex. Acetylcholine (1 µg./kg.) was injected into the ipsilateral carotid artery after A. Key: A = control; B = enhancement; and C = recovery

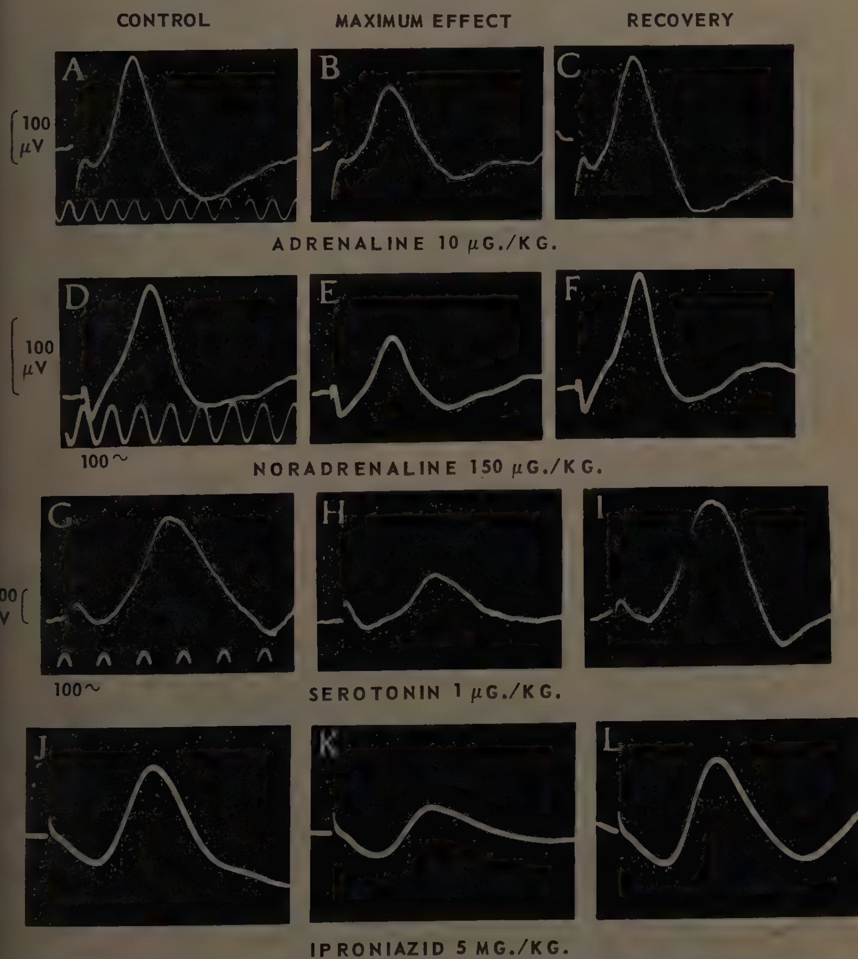


FIGURE 2. The natural cerebral synaptic inhibitors and antimonoamine oxidase.

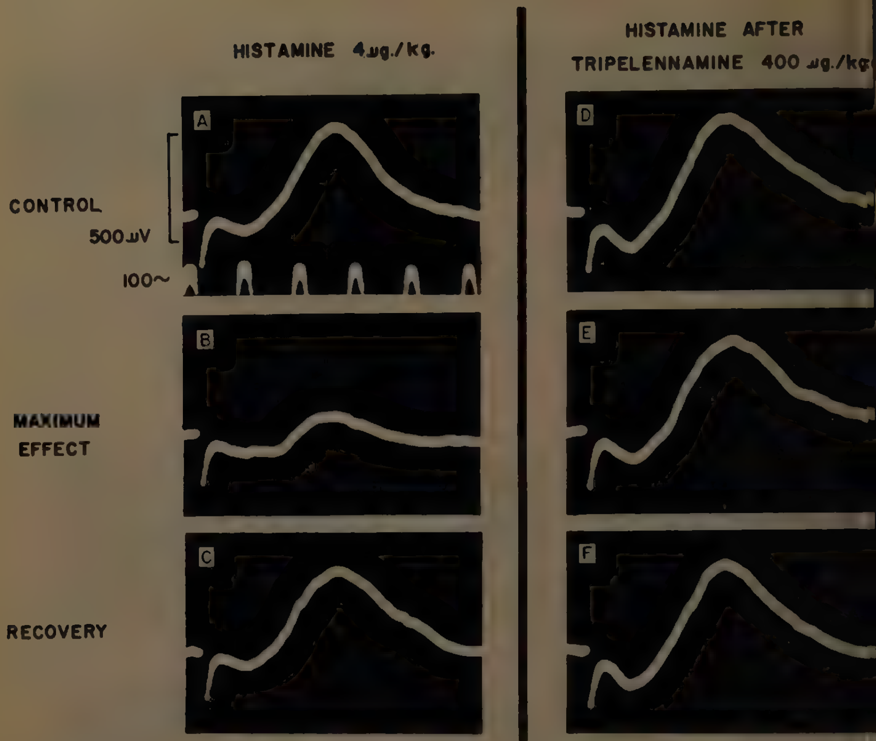


FIGURE 3. The prevention of histamine inhibition by tripelennamine in an intercortical (transcallosal) system. The potentials were evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every 2 sec. The injections were made in the ipsilateral common carotid artery.

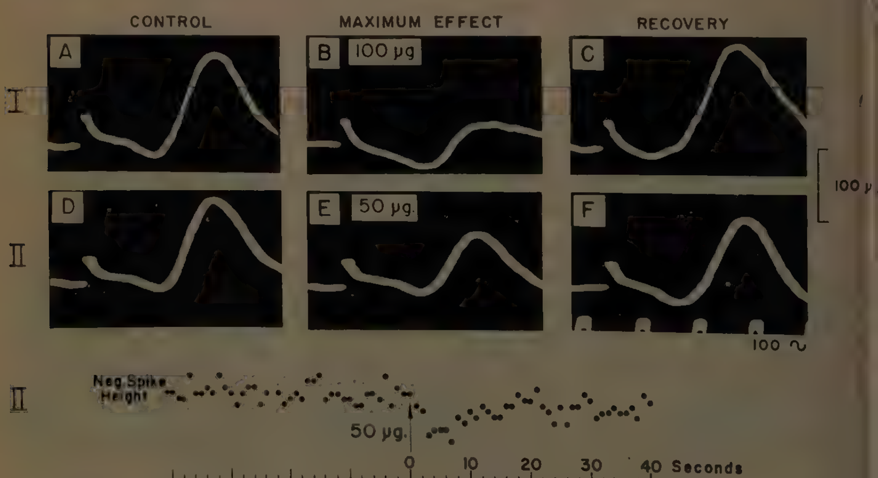


FIGURE 4. Cerebral synaptic action of gamma-amino butyric acid (GABA) in an intercortical (transcallosal) system. The potentials were evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every second. The GABA was injected into the ipsilateral common carotid artery.

is not the only end result possible. In fact, inhibition can secondarily lead to increased activity. This can be shown at the synaptic level by resorting to more complex networks. Thus we have proved that LSD-25 and serotonin enhancement of potentials evoked in the primary optic cortex by stimulation of the geniculocortical fibers in the lightly anesthetized cat, while the transcallosally evoked potentials in the optic association cortex are inhibited simultaneously (FIGURE 7, *left*), is actually a release phenomenon due to inhibition of a corticogeniculate tract.[8] This is itself an inhibitory tract and one of the pathways for cortical restraint of subcortical structures, in this case the lateral geniculate ganglion. FIGURE 8 shows the pathways and the fact that the syn-

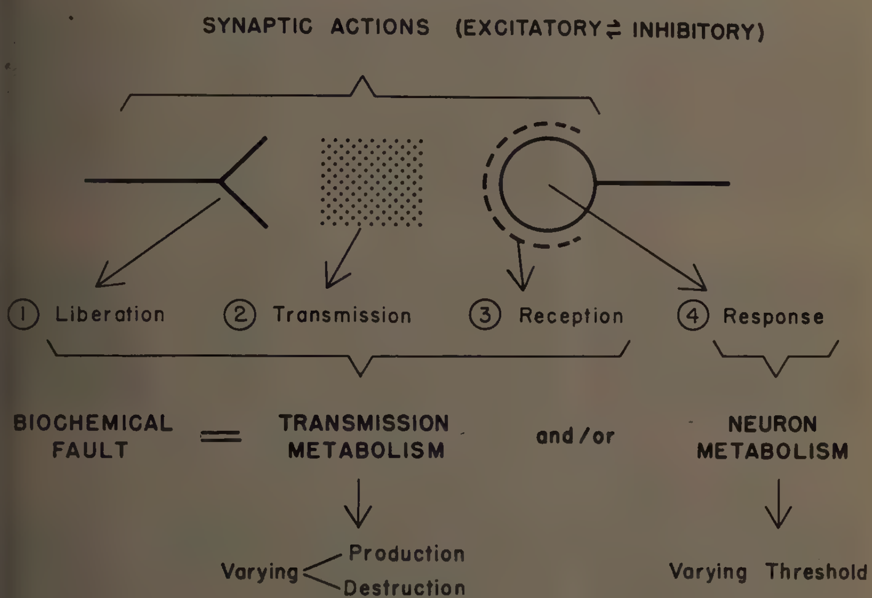


FIGURE 5. Potential factors in disturbed synaptic equilibrium.

apses in the association area are almost exclusively axodendritic, while those in the primary optic cortex are axosomatic with a few assumed to be axodendritic. Confirming the interpretation advanced, interruption of the corticogeniculate tract prevents the release phenomenon described and reverses the enhancement of primary optic evoked potentials by LSD-25 to a simple inhibition, identical to that observed in the exclusively low threshold axodendritic synapses of the optic association area (FIGURE 7, *right*). Larger doses of LSD-25 include in their action the higher threshold axosomatic synapses, which predominate in the primary visual pathway and thereby mask the enhancement, secondary to release, converting it to an uncomplicated inhibition without the necessity of physically interrupting the corticogeniculate tract.

It becomes increasingly clear how inhibition directly and by release can produce its complex manipulation of patterns. Emphasis is also placed on an important if somewhat subtle distinction between the concept that chemical

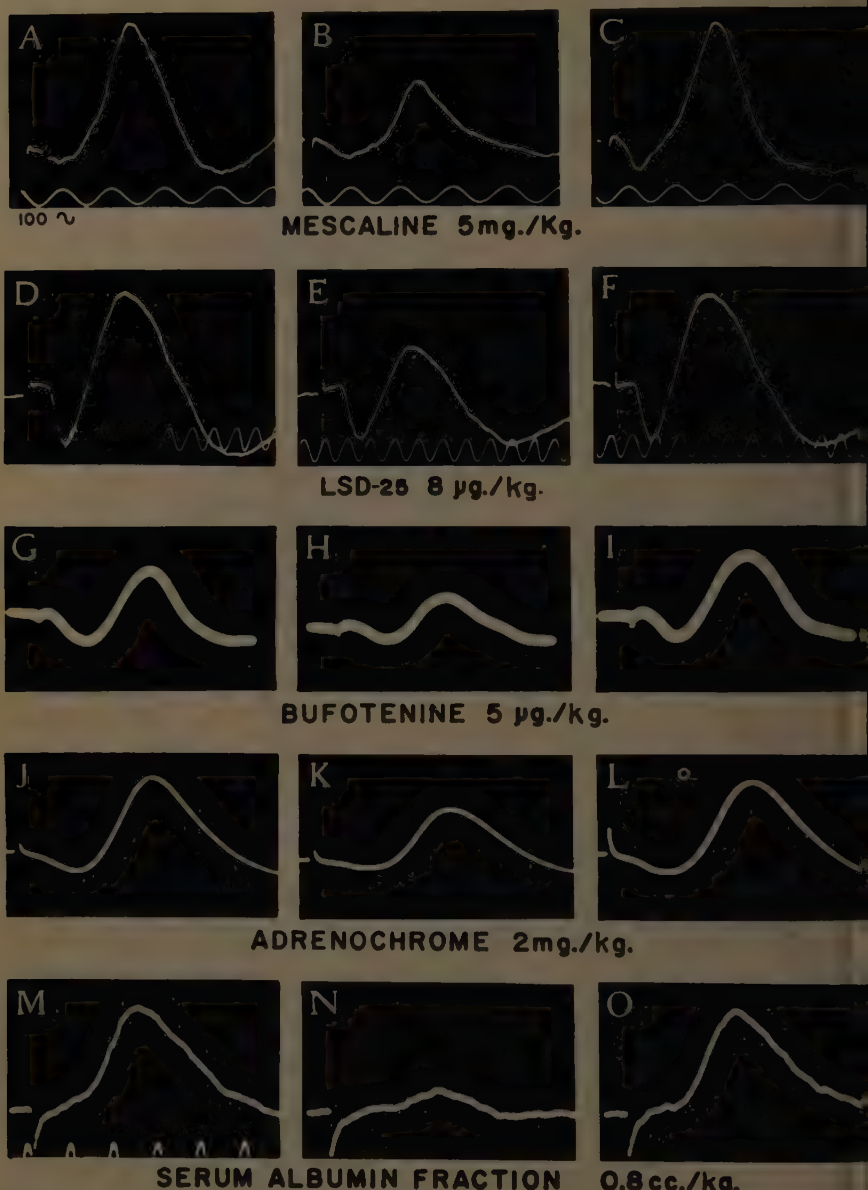


FIGURE 6. Unnatural cerebral synaptic inhibitors in an intercortical (transcallosal) system. The potentials were evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every 2 sec. The injections were made in the ipsilateral common carotid artery.

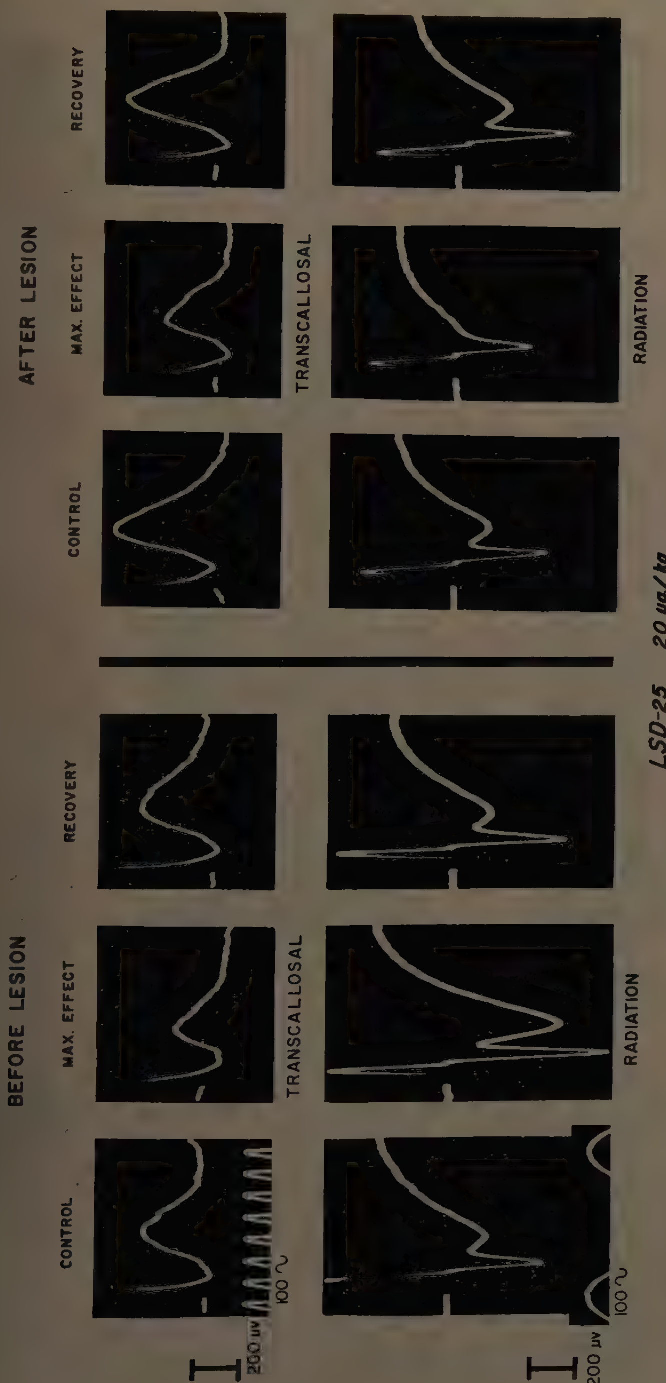


FIGURE 7. Reversal of the chemical effects in the geniculocortical system by lateral geniculate destruction. The cortical potentials were evoked alternately every 2 sec. through the transcallosal and optic radiation fibers. Pentobarbitalized cats were given ipsilateral common carotid artery injections.

and drug effects are universal in the synapses involved and identical in kin[d] with the observed differences stemming from threshold differences, and wit[h] the less-justified concept of localized specificity at selective sites. The tw[o] concepts describe the same phenomena, with the latter regarding the differ-ences as qualitative and the former regarding them as only quantitative: a[n] analysis that is in keeping with classic pharmacology.

In these ways a unitarian explanation of psychotogen action, inhibition in it[s] various forms, suffices to determine the observed synaptic effects. It remain[s] to examine the even more complex patterns that constitute overt behavior i[n]

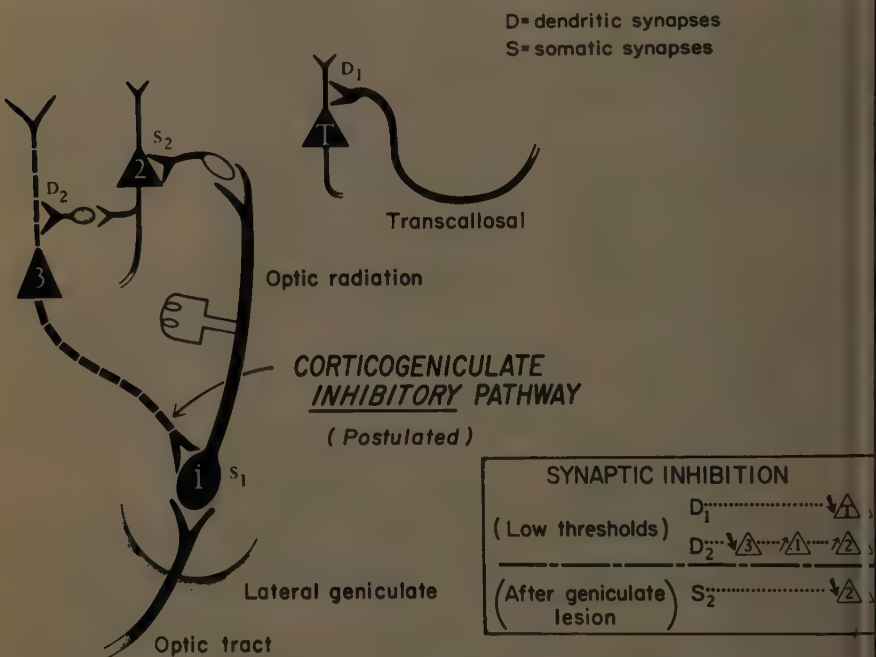


FIGURE 8. Schematic pathways that illustrate the release phenomenon from dendriti[c] synaptic inhibition in the optic system.

animals and man. Ultimately, it is human behavior that is of major interes[t]. Exaggerated behavior often offers revealing clues, so we are mindful of th[e] distortions of behavior, resembling aspects of mental disturbance, that the exog-enous psychotogens produce; and that these, as well as the natural disturbance[s] or clinical conditions they resemble, are controllable by tranquilizers. Our in-terest in pathology, both as the condition requiring therapy and as the exag-geration that illuminates the normal, has the additional advantage of highlight-ing the fact that such restorative processes as tranquilization can be adequatel[y] studied only when pitted against abnormality. This is well exemplified by th[e] familiar antipyretics that, in doses that dramatically bring down fever tempera-ture, have no detectable effect on normal temperature.

We have therefore pitted tranquilizers against psychotogens and serotoni[n]

and have found, in accordance with a prediction relating synaptic inhibitory action and exogenous psychotogens to clinical mental disturbance, that tranquilizers do antagonize the exogenous psychotogens, as demonstrated by the reduction or prevention of synaptic inhibition by prophylactic administration.[9] One example is presented in FIGURE 9. This result was accomplished with doses of tranquilizers that per se did not alter synaptic performance, as evidenced by lack of change in the control potentials. Much larger doses given alone, how-

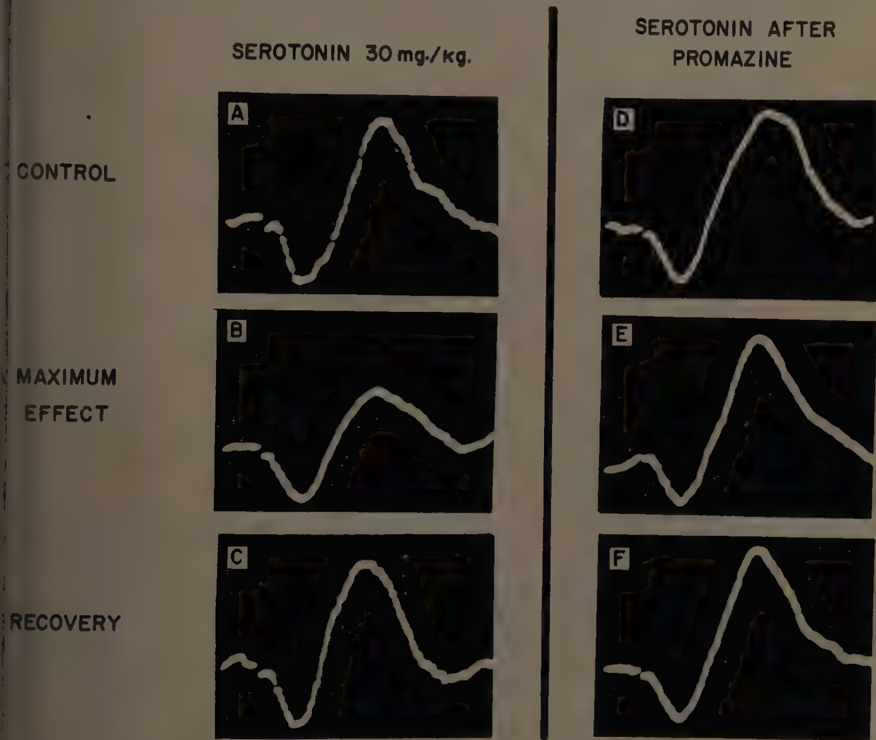


FIGURE 9. Prevention of the serotonin effect by promazine in an intercortical (transcallosal) system. The potentials were evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every 2 sec. Injections were made in the ipsilateral common carotid artery.

ever, afford insight into the nature of the tranquilizer actions. They produce an inhibition qualitatively similar to that of the neurohumoral inhibitors or the psychotogens. Similarly, clinical overdosage of tranquilizers also produces symptoms of psychosis. We are led to conclude that the tranquilizers we have studied in this way are indeed weak synaptic inhibitors that owe their protective action against strong inhibitors, such as serotonin and the exogenous psychotogens, to their competition for the same site of action or the same receptors. Successful pre-empting of receptors by the tranquilizer substitutes a weak or negligible inhibition for a strong psychotogen-induced inhibition, unless too much of the tranquilizer is used. The different situation presented by non-

specific depressants, such as the barbiturates, is expressed in quantitative term by the equality of protective and depressant doses, that is, protection withou reduction of synaptic transmission is not possible for simple sedatives but is th property of tranquilizers.

We are now ready to ask whether behavioral patterns appear to be deter mined by inhibition and its consequences in a fashion paralleling the synapti A simple and profitable measure of behavior has turned out to be the cond tioned approach for a water reward on a tone signal to the thirsty rat. Th stimulus-response latency or reaction time is indicated in the record shown i FIGURE 10 by a pen that starts traveling up on the presentation of a signal an stops on the pressing of the reward lever, which also terminates the cycle. Th diagonal marks on the lower line indicate achievement of reward. A latency o over 20 sec. terminates the cycle without reward. Recycling takes place on variable-interval schedule.

Under these circumstances, intraperitoneal administration of LSD-25 in hibits performance, prolonging latency to the point of no reward (FIGURE 10 line 3). As in the synaptic experiments, a dose of tranquilizer such as chlo promazine (CPZ), that is per se without effect on performance (line 2), whe given before the LSD-25 greatly abbreviates the LSD-25 inhibition (line 4 that is, it successfully antagonizes it.[10] Pursuing the parallelism to the synapt situation, larger doses of CPZ were used, as shown in FIGURE 11. Line 1 show that a larger dose that still falls short of effect on control performance, instea of reducing the LSD-25 inhibition (line 2) enhances it (line 3); a still larger do inhibits on its own, without any LSD-25 (line 4). In this way we see agai that a weak inhibitor can block the effects of a stronger one, or can, if present i sufficient quantity, make itself evident by inducing straightforward inhibitio in its own right. A water extract of Kava root, which behaves like LSD-2 synaptically, also behaves like it in the conditioned approach testing.[7]

A more complex and very interesting situation is afforded by imposing th requirement that the subject discriminate between and choose the correct of tw signals before the reward lever can operate, thus terminating the cycle an delivering a reward if it was paired with the correct stimulus. The signals a two different pitched tones for the rat and two different colored lights for th monkey. In each cycle alternate self-presentation of stimuli is made possib by pressing the signal lever. Small doses of LSD-25 (FIGURE 12), mescali (FIGURE 13), and amphetamine (FIGURE 14) produce little change in the correct ness of reward lever pressing, but increase manifold the self-presentation stimuli associated with and evidently necessary for arrival at this performanc We feel this means that inhibition has impaired ability to select or "decid upon the correct signal.[11] Larger doses block performance altogether, whi the intermediate steps are illustrated by the amphetamine (FIGURE 14), whic shows the greatest increase in self-presented stimuli with a small dose (line and the disappearance of this effect with a larger dose that is short of a blockin dose, (line 3).

These data are in contrast to a nonspecific depressant such as Nembuta which in nonblocking doses slows down performance, as reflected in the opera tion of both stimulus and reward levers. In larger doses there is some increa

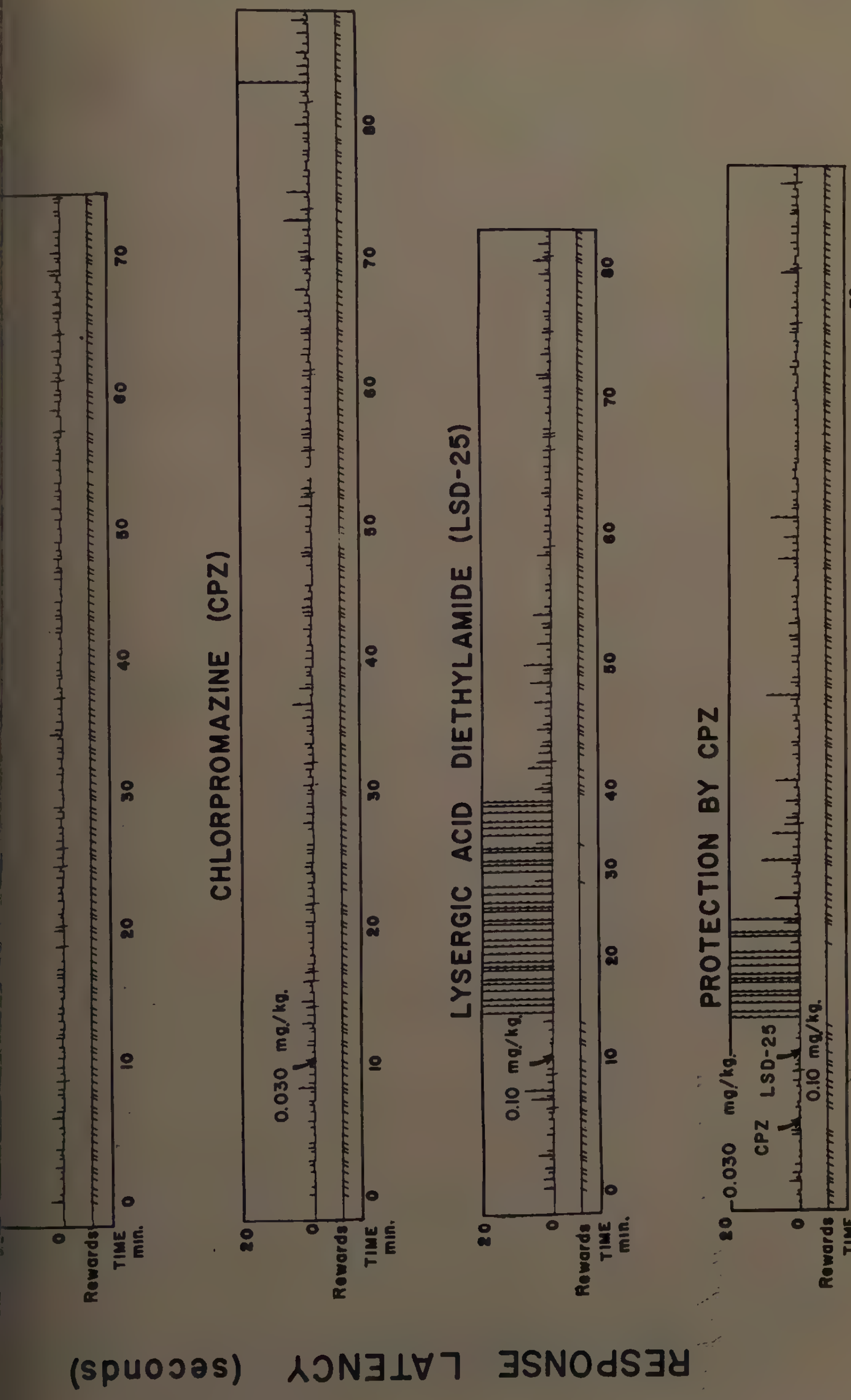
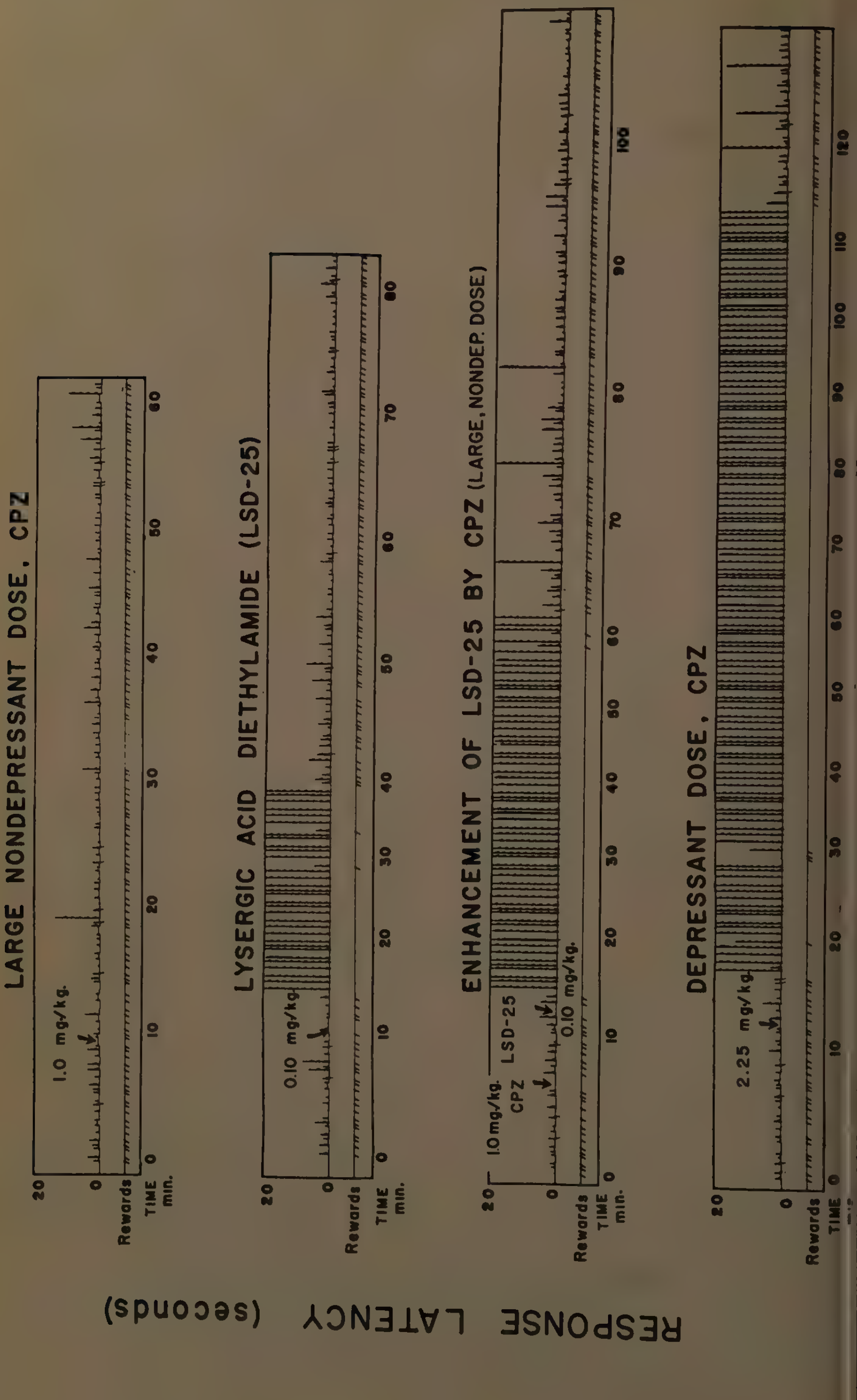


FIGURE 10. Lysergic acid diethylamide inhibition and chlorpromazine protection effects on the approach behavior of the rat (Rat J-3).


LARGE NONDEPRESSANT DOSE, CPZ
1.0 mg/kg.
LYSERGIC ACID DIETHYLAMIDE (LSD-25)
0.10 mg/kg.
ENHANCEMENT OF LSD-25 BY CPZ (LARGE, NONDEP. DOSE)
1.0 mg/kg.
CPZ
LSD-25
0.10 mg/kg.
DEPRESSANT DOSE, CPZ
2.25 mg/kg.
Rewards
TIME
min.
RESPONSE LATENCY (seconds)

in the number of self-presentations, but the pressing of both levers is greatly slowed down. Finally, in still larger doses there is complete block.

Although, of course, the actual location and number of synapses at which the drug action responsible for the behavioral results is taking place is not identified by these studies, the parallelism between the drug responses in the synaptic and behavioral experiments suggests that inhibition is determining performance in the same manner. We are presently engaged in an attempt to translate from animal to human behavioral experiments. The operant conditioning studies described above are now being carried out in man.

Reflection on the lower threshold to the inhibitory action of exogenous psychotogens of the association areas, as compared to the primary receiving areas, has caused us to think that the resulting dissociation of information handling areas, because of the reduced access to stored information in the association or reference area, would make for perceptual misjudgments and difficulty in reality

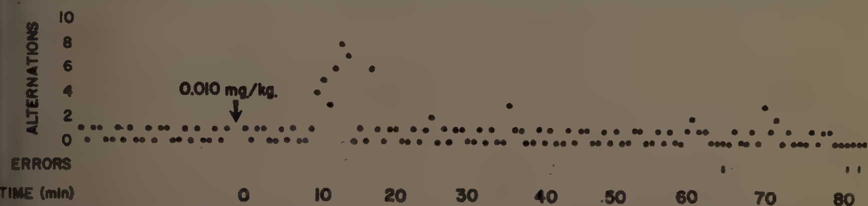


FIGURE 12. Effect of lysergic acid diethylamide on the stimulus-selection behavior in a two-choice situation in the rat.

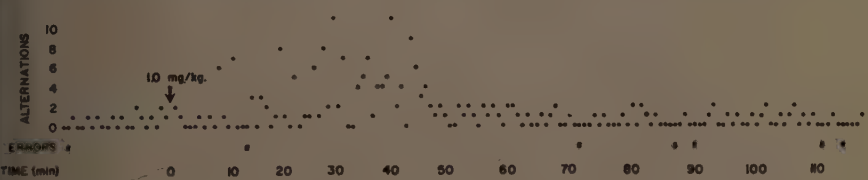


FIGURE 13. Effect of mescaline on the stimulus-selection behavior in a two-choice situation in the rat.

testing, which could constitute a mechanism for hallucination that is determined, in this instance, by inhibition. This neuropharmacological theory of hallucination[8,12] is being tested by measuring the threshold for perceptual misjudgments in the form of visual illusions that are normally experienced; the quantified change in this threshold is induced by LSD-25 in subclinical doses that produce no overt symptoms. It is hoped in this way to test the concept of hallucination and the possibility of using this perceptual testing as a clinical yardstick for diagnosis, for assessing clinical status and for measuring response to therapy.

Summary

We have presented data to illustrate that inhibition, both synaptic and behavioral, can be the determinant of a variety of patterns encompassing both directions of change possible to cell function in general and to neural function in particular—increase and decrease—the former as an indirect effect (release phenomenon) and as a consequence of the direct one, which accounts for the latter.

[FIGURE 14. Effect of a low and a moderate dose of amphetamine on the stimulus-selection behavior in a two-choice situation in the rat.

Emphasis has been placed on the advantage of studying function through the exaggerated manifestations of dysfunction and the effectiveness of corrective agents in inadequately compensated dysfunction, compared to the immunity of normal function. Restoration of equilibrium may result from competition of inhibitors for their receptor sites. When restoration is accomplished by antagonizing a psychotogen, this may be regarded as a step in the direction of cure even if, because of inability to eradicate a biochemical fault, the therapy must be maintained. If the possibility is entertained that distorted patterns of pathology may be "learned" and thereby entrenched and perpetuated, then any form of interruption, such as shock, tranquilization, or psychotherapy, may be thought to break this vicious cycle and contribute to cure by allowing the extinction of unwanted patterns and the relearning of normal patterns. It can be hoped that partial restoration can permit overtaxed compensatory mechanisms and other defenses to resume control and maintain a normal or nearly normal equilibrium. The counterpart of inhibition in this equilibrium, excitation, also exercises direct and indirect actions on synaptic and behavioral patterns; it can likewise be the focus of pathology requiring specific antagonism of excitation or a corresponding enhancement of inhibition.

Susceptibility to inhibition of association or reference areas has been made the basis for a theory of hallucination, whose testing may lead to a clinical yardstick for inadequate integration and its amelioration.

Biological systems are composed of units capable of two-directional changes. These binary systems, multiplied and strategically related and timed, can account well for observed behavior in all its richness and exquisite variety.

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ON THE RELATIONSHIP BETWEEN NEUROPHYSIOLOGY, PSYCHOPHYSIOLOGY, PSYCHOPHARMACOLOGY, AND OTHER DISCIPLINES

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Ultimate Goals

Sholom Aleichem relates the story of the young Talmudic scholar who spo weeks poring over ancient manuscripts, barely interrupting himself for the fo and drink that was brought to him. Very suddenly on a morning of the th week, a look of great joy suffused his features and he dashed from the emp synagogue into the streets, shouting "I have the most wonderful answer; som body ask me a question!"

We find ourselves with a similar embarrassment of riches: even in this br monograph we have answers in neuroanatomy, neurology, neurophysiolog electrophysiology, psychophysiology, psychopharmacology, neuropharmac ogy, psychology, and psychiatry. The plethora of answers leads one to as What is the question, and why are there so many answers? The ultimate pro lem we are seeking to solve is: "How can we describe, explain, predict, and co trol human behavior?" The multitude of answers arises from attempts to de with one or another or a third or a fourth aspect of the behavior of organism

How Various Answers Relate to Each Other

What do the squiggles on an electroencephalogram have to do with soc prejudice? Is it meaningful to relate level of aspiration to 17-ketosteroid ou put? Perhaps if we can clarify the manner in which the various answers a related to one another we may see new possibilities and, at least, clear up som of the rampant confusion.

The Universe of Discourse

The variety of answers we have, the data describing them, and the even themselves do *not* bear a fixed and permanent relationship to one another. T relationship between one event and another is determined by the question are asking. Thus the same two events (although they may remain identi and fixed in time and space) may be intimately connected if we ask question only tangentially connected if we ask question B, and completely nonreleva in respect to question C. For instance, (A) you and I stand in the intima relationship of speaker to listener or author to reader, in terms of our soc behavior; (B) our individual oxygen consumption and carbon dioxide excreti remotely relate the two of us, since we utilize a common air supply; and (under normal circumstances my individual thyroid iodine uptake is not affect by your thyroid function.

The term "universe of discourse" is a somewhat more precise manner answering the question: "What are you talking about?" In general, such a u verse consists of events describable within a single frame of reference, of t same order, and of such regularity of occurrence as to appear relatable to ea other.

When the universe of discourse is assumed to be known. In daily life it would be tedious and pathological to require that we define our universe of discourse each time we speak. As a rule, there are more than sufficient clues to determine in what universe we are communicating. If, as we are leaving a session of this conference, I were to ask: "Where are you going?" you would understand that I was referring to your immediate physical objective, and not to some goal in life toward which you are striving.

The same assumptions are sometimes made in science, and this is particularly true in areas involving the type of behavior we are apt to discuss in ordinary nonscientific conversation. In chemistry or electrophysiology the language, as well as the concepts, identify the universe of discourse. At times, however, utilizing the language and concepts of everyday speech, we assume that the universe of discourse of a scientific question is known.

For example: What is the basis for seizures?

Normally one may expect the answer to such a question to be in the universe of discourse of electrophysiology and/or neurochemistry. Explanations based, for instance, on the psychoanalytic theory that seizures are actually symbolic orgasms, would satisfy only under very special conditions. On the other hand, almost everyone would agree that psychological factors* might influence or precipitate attacks.

For example: What is the basis for delusions of grandeur?

One should normally expect an answer to this question in terms of psychological needs and mental mechanisms. Our scientific expectations are such, however, that if the delusions of grandeur were those occurring in syphilis of the central nervous system we should not be too surprised to have their occurrence explained as a result of "arteriolar cuffing and loss of cells in the frontal lobe."† The inadequacy of this purely physiological explanation is that, as stated, it gives no indication of how or why the specific somatic changes produce the specific psychological effects.

When the universe of discourse is ambiguous. We may ask, for example: Why do the phenothiazines reduce the hyperactivity of manic patients?

There are two "normal expectations," each of which involves a different universe of discourse: one is that the drug influences the psychological mechanisms (reduces psychic energy or relieves anxiety‡); the other expectation is that the drug acts on the neurophysiological mechanisms to reduce the amount of motor activity directly.§ We frequently weasel out of committing ourselves to one or the other universe of discourse by saying that the drug acts as a

* The influence of psychological factors on physiological ones properly should be called psychophysiology.

† The influence of physiological factors on psychological processes properly should be called physio→psychological, but the term psychophysiological is customarily used to cover actions in either direction. It would be useful to indicate the direction; for example, psycho→physiology, or psycho←physiology.

‡ The influence of drugs on psychological behavior is usually called psychopharmacology. We should indicate the direction of activity here also. In the present example it is obviously psycho←pharmacology. Psychological states can also influence the activity of drugs, in which case it would be psycho→pharmacology.

§ The action of drugs on the responses of the nervous system is usually referred to as neuropharmacology, and again the direction of activity should be indicated. In this case it is neuro←pharmacology. The term neuropharmacology should not be used if reference is made to psychological reactions.

"sedative." Unless more fully explicated, the use of the word "sedative" is merely an euphemism for "reduction of hyperactivity."

Are these alternate explanations disjunctive (that is, if one is true, must the other be false)? Or are the alternate explanations in some sense complementary (that is, do the neuropharmacological and the psychopharmacological explanations state two different facets of the same identical effect)? Or are the alternate explanations nonrelevant to each other (that is, that no meaningful relationship exists between the two explanatory concepts)? Certainly these three possibilities themselves are disjunctive (since all three cannot be true.) Failure not only to determine which is correct but even to discriminate between them in a source of endless confusion. The same three alternatives exist in respect to such questions as the cause of akathesia in patients on phenothiazines, the increased activity of patients on psychic energizers, and the occurrence of extrapyramidal symptoms with ataraxics.

From the foregoing we can derive an important generalization, the "Law of Answers": *We must answer a question in the same universe of discourse in which we ask it.*

When the universe of discourse is stated or clearly inferable. Example 1 (neurophysiological): Are there regular pathways utilized in the spontaneous electrophysiological activity of the brain?

Example 2 (neuro→pharmacological): Is the differential effect of amphetamines on different people, or even on the same person at different times, related to the neurophysiological state of the individual as measured by reaction time?

Example 3 (neuro←pharmacological): Do monoamine oxidase inhibitors increase the electrophysiological activity of the brain as measured by the toposcope?

Example 4 (pharmacological): In what way does lysergic acid alter the metabolism of tryptophan?

Example 5 (psycho→pharmacological): both A. Wikler and V. A. Kral (personal communication, 1960) have shown that barbiturates can cause either enhanced group participation, or sleep, depending on the psychosocial situation. Is the action of heroin affected in the same manner?

Example 6 (psycho←pharmacological): Can a drug, IKONSD,* completely relieve both obsessive and compulsive symptoms?

Example 7 (psychological): Is the "autobiographical therapy" used in the Soviet Union similar in technique to the "active" psychoanalytic method used in the United States?

Example 8 (psycho→physiological): Do auditory hallucinations produce measurable changes of electrical activity on the auditory cortex?

Example 9 (psycho←physiological): Would placing a subject (normal or abnormal) inside a giant induction coil alter his psychological state?

Obviously these are examples of only a few of the possible universes of discourse, but they are the ones with which the contributors to this monograph are most frequently concerned (although, perhaps, we should also add psycho→social, psycho←social, and sociological universes).

* *I Know Of No Such Drug.*

The Concept of a Hierarchy of Levels: Origin and Limitations

The usual cliché of thinking is to construct levels of hierarchies. The psychological level or universe usually falls somewhere in the upper half, with the sociological (cultural, economic, political, religious) level above it and the somatic (physiological, chemical, atomic) below in descending order. Although there may be occasions when such a systemization is useful, it is far too artificial and rigid to be accepted as an "ultimate" reality. As previously indicated, the universe of discourse may cut across entirely different planes (for example, genetics), and certainly the areas "between" such levels (such as psychophysiology and neuropharmacology) are as truly universes of their own as are psychology or physiology.

Sociology could not exist without people and their psychological behavior. In turn, psychology could not exist without the universe of physiology as part of the environment. Physiological processes involve certain chemical reactions that normally are "assumed," since they occur regularly and uneventfully. Chemistry, in turn, presupposes the sensible behavior of atoms, molecules, electrons, and the like.

In theory (at least) physics could exist without chemistry, chemistry without physiology, physiology without psychology, psychology without sociology. This provides the temptation to say that sociology is really nothing but group psychology. Pavlov at one time (1957) stated that psychology was really only physiology; later he laid increasing stress on the "second signal system," that is, on psychology. The biochemist often regards the physiologist as a flighty fellow not dealing in the really basic issues, while theoretical physicists have greater contempt than any other group for the intellectual pursuits of the rest of mankind. This unidirectional dependency is what has given rise to the hierarchy.

Another reason for the hierarchy is that, when we think or feel, it is almost certain that some sort of brain activity occurs. The fact that psychological processes are accompanied by neurological ones does not mean that the psychological processes are fully understandable in terms of neurophysiology and/or neurochemistry. Almost the reverse is true: those parts of neurophysiology or neurochemistry involved with or concerned with thinking and feeling would be incomprehensible unless we knew psychological processes were going on; although we could follow the disparate neuropsychological or neurochemical activities that did not involve thinking and feeling, the larger patterns of change would be meaningless unless we were aware of the "intrusion" and could relate it to the "level above."

A third factor involved in support of the hierarchy is the fact that implementation of thoughts and feelings (through behaving) again involves neurological and biochemical mechanisms. As with the thinking and feeling itself, reference must be made to the psychological level to understand the somatic reactions.

The establishment of universes of discourse is an arbitrary device but, in so far as they mean something, they *do* have parameters and laws and theories, and they are not all reducible to some other universe of discourse. Hydrodynamics is *not* reducible to the chemistry of H_2O . Psychological processes exist

in their own right and *do* alter physiological (and hence, biochemical and atomic) states.

Thus, in conclusion, there is no "fixed" paradigm for universes of discourse and the relationship of one universe of discourse to another depends on the question asked.

The Intrusion of One Universe of Discourse into Another

There are certain events, laws, and factors that are best understandable per se in one particular universe of discourse (B), but that "intrude" into another universe of discourse (A) under investigation. It is not necessary, because of this, to explain Universe A in terms of Universe B. It is sufficient merely to state the nature of the relevant "intrusion" and what its effects are in terms of universe A (not in respect to B, its own universe).

For example, in tracing the psychodynamics of a patient as he recovers it may be quite relevant that he received a particular drug. The effect of the drug (perhaps it was a psychic energizer) in the psychological universe of discourse is of concern, whereas the chemical properties of the drug (that it was an MAO inhibitor) is unimportant. The latter property has relevance in a different universe of discourse.

Consider another slightly more complicated example in the universe of neuro←pharmacology: an investigator is interested in the effect of reserpine on the reticular activating system (RAS). It is found that taking reserpine placebos also leads to an increase of activity of the RAS. Must one then shift the investigation to a full-scale study of the symbolic significance of pills to patients? Of course not! The nature of the "intrusion" should be determined by asking, for example: What is the magnitude of the placebo effect? How long does it last? Does it recur? The extent of such action on the reticular activating system is then taken into account in the final evaluation.

From this we can derive another useful generalization, the "Law of Intrusion": *when an event intrudes from elsewhere its effects should be described in terms of the universe of discourse under study and not in respect to its primary discipline.*

The Environment and Its Limits

At times, events that are part of a universe of discourse are allowed to "slip out" and are treated as though they were part of the environment or are ignored.

Thus in describing psychodynamics, the "placebo effect" might be referred to as though it were in the area of pharmacology. Conversely, at times part of the environment is improperly incorporated into a universe of discourse.

For example, anxiety (which may be an "intruding" factor and certainly has its correlates) is treated as though it were a neurophysiological condition.

Either of these errors can cause great subsequent confusion, since the occurrence of regularities in a universe of discourse is of the essence of science: if the universe is arbitrarily limited, apparent "laws" may be found that omit essential data. On the other hand, the inclusion of "foreign" (environmental) data may preclude the finding of regularities that otherwise would be obvious. We

may, therefore, state a "Law of Environmental Limits": *the environment (which includes certain events from other universes of discourse) must be sharply differentiated from the universe of discourse that it limits.*

The Role of the Environment

No universe of discourse exists in isolation. Even when not "intruding," events occurring in one universe are often essential to the maintenance of other universes. Neither neurophysiological nor psychosocial behavior normally makes reference to kidney function, yet neither could long exist without adequate urinary excretion. In addition to the biological universes of discourse there exists the external environment, which is not essentially different in this respect. We assume that there will be adequate oxygen, that gravity will continue to function, and that those conditions necessary for the maintenance of the status quo will continue without interruption. It is usually only when one of these becomes disturbed in such a way as to alter directly the functioning of the universe of discourse we are describing that we speak of an "intrusion" or an "alien factor." Under ordinary circumstances we should not enumerate all the other events in the world that are necessary to the continuation of the universe of discourse in which we are dealing. To include such a description implies that there is or may be a special relevance, and we can thus distract from, rather than augment, the description.

These statements may be formalized in a "Law of Environmental Support": *although the environment is necessary for support and maintenance of a universe of discourse, it need only be described if unusual, deviant, or of special relevance.*

Scientific "Proof"

This article is not a general treatise on the nature of scientific methodology but, nevertheless, certain cautions are in order. In point of fact, we are never able to "prove" anything; we can only accumulate more and more evidence that our hypothesis is not *in*correct. There are a number of ways of doing this; although some of the methods are contributory they are not, of themselves, sufficient.

Explanation Is Not Sufficient

To explain, *post hoc*, what psychodynamics were involved or how a molecule broke down to produce a particular effect, can be done in dozens or hundreds of different ways. If mere explanation were sufficient, all of these ways would be "true." The fanciful manner in which chemical formulas are sometimes drawn to show a presumed relationship to other chemical formulas is as imaginative as anything in psychoanalytic theory. Embellishment, "interpretation," or extension of a theory to meet the nonconforming case is usually a reason for suspicion and closer examination.

Regularity Is Not Sufficient

Because a certain event in, let us say, the psychological area regularly follows or occurs simultaneously with a neurophysiological event is no proof that the two are directly—or even indirectly—related. Such a correlation certainly

constitutes an invitation to investigate if there is a common causal nexus, but a theory relating the two is suitable only as a working hypothesis. All too often we have been told that this or that chemical (or sociological factor or electrophysiological event) is the *cause* of some mental state or feeling tone, simply because the two were associated. Even the existence of such pairings has usually been shown to be false when more extensively and intensively investigated.

Replication Is Not Sufficient

One of Koch's postulates is widely misunderstood and abused. It is not sufficient to be able to induce or replicate part of a disease; the entire natural history of the disorder must be reproduced. For instance, to stimulate the globus pallidus and produce symptoms of parkinsonism does *not* prove that a disorder of the globus pallidus is the cause of the disease. This nucleus may be involved only as an intermediate step, or may not be involved in the causal chain at all, and the fact that stimulation reproduced certain symptoms may be artifactual. Similarly, the chemical structure of drugs that are known to produce psychoticlike behavior is no demonstration that a similar type of chemical structure occurs in the human patient and produces mental disorder. The fact that electrical activity of the reticular activating system is markedly different during sleep, wakefulness, and under a variety of specified conditions does *not* of itself prove it is the alertness center of the brain. It, too, may only be part of the causal chain, or it may be coincidentally involved. All of these findings are, however, invitations to further investigation, since they constitute preliminary but insufficient "proof."

Control Is Not Sufficient

A patient is treated by a psychiatrist who believes in Pavlovian theory (or Freudian theory or Jungian theory) and who uses techniques compatible with his theory. The fact that the patient recovers does not constitute a "proof" of the psychiatrist's beliefs. The same holds true in the more "exact" disciplines. Many chemical reactions were well controlled on the basis of alchemy with its astrological theories, and the phlogiston theory was the basis for much practical work. An ability to control predicated on a particular hypothesis, although it is not sufficient in itself, does, however, tend to lend support to a theory.

Even Prediction Is Not Sufficient

At the core of the scientific method is the ability to predict, and if this is done with two special qualifications observed it is the strongest evidence that we can educe for correctness. The first qualification is that the prediction must be in respect to an irregularly occurring, rare, or new event. The other qualification is that the prediction should be dysjunctive, that is, that various incompatible alternative possibilities are enumerated and the ones that will *not* occur, as well as the one that will occur, are specified.

Hence it is not sufficient to say that if a patient has a severe psychic trauma his condition will change. Specifically, what he *will* do and what he *will not*

do must be described. Similarly it is not sufficient to say that "the addition of copper and other trace metals will change the effect of the phenothiazines," nor does the statement "stimulation of the septum pellucidum will change the electroencephalogram" mean nearly as much as it would if the disjunctive possibilities were enumerated and the correct one predicted.

It should be emphasized that while the last-named aproach is the most desirable, there are many occasions in which theory is not adequately developed nor techniques available for proceeding in this manner. Under these circumstances it is perfectly legitimate to base our working hypothesis and our practice on such evidence as is available. We should, however, strive to develop theory and technique to the point at which new and disjunctive events are predicted and their occurrence empirically verified.

The Binoculars Are Not the Landscape

We may use drugs to investigate neurophysiology, electroencephalograms to test sociological hypotheses, and conditioned reflexes to confirm theories of existential psychiatry. The universe of discourse in which a technique occurs is relevant only in so far as it bears on the information obtained.

Thus a theory has been advanced that obsessive compulsive behavior is due to reverberating circuits in the brain. If this is true, drugs blocking synaptic transmission might cause a remission. The use of drugs for this purpose does not place the research in the pharmacological or psychopharmacological universe of discourse. Actually the drugs are being used to test a psychophysiological hypothesis.

We may, therefore, state the "Law of Technique": *the technique used to obtain information does not necessarily determine the universe of discourse in which it is to be used.*

Description, Explanation, and Lawfulness

Within a Single Universe of Discourse

Within any one universe of discourse there exists an infinity of events to describe and an even greater number of ways of doing the describing. Descriptions need not be either complementary or contradictory but (as earlier illustrated) may be nonrelevant. As a rule, a descriptive system should strive to be exhaustive for the relevant events in the field while it is discrete and differentiated enough to apply to the individual case. The explanatory concepts similarly aim at the largest possible scope compatible with reference to the individual states. Obviously such things as self-consistency and commensurability with general scientific theory are assumed. All else being equal, Occam's razor* should be applied; however, if it is applied too closely it may not only shave but may also cut a throat.

Between Universes

Identity of explanatory concepts. In our effort to describe, predict, and control human behavior we are constantly searching for descriptive techniques,

* *Entia non sunt multiplicanda praeter necessitatem* (entities ought not be multiplied except of necessity).

concepts, and laws that will unite one universe of discourse with another in an effort to interrelate all the universes. An obvious and sometimes successful method is to find an explanatory concept that is identical in two different fields. If a drug were to cause "excitation" (that is, increased activity) in both the electrophysiological and the psychological universes of discourse, it would greatly aid our comprehension of what was happening. If some other drug were to cause a decrease of activity, both in terms of electrophysiological and psychological universes, we should have some elements to begin building a broader explanatory concept. If it were found that these same two drugs acted respectively to speed up and to slow down certain chemical processes, the breadth of the explanatory concept would again broaden.

Such an approach is not without its monkey traps, since the similarity of concepts may be apparent rather than real. A horrible example of this is "depression," which in electrophysiological or neurochemical parlance means a dampening or decrease of amplitude or frequency, whereas in the psychological area the primary reference is to an affective state. The fact that in this affective state there is sometimes a decrease of physical and mental activity has led to an assumption of identity, which is partial rather than complete and, therefore, deceptive. Similarly the words "tension" and "stress" are used in a variety of fields in the vague hope that there is an identity of concept, whereas in point of fact the isomorphism is probably slight.

Relationship between generalizations. Up to the present time the most useful procedure has been to find relationships between the generalizations of one universe of discourse and those of another. Sometimes generalizations can be made about the generalizations; in this way the fields may be interrelated.

Expansion and reorganization of the universe of discourse. The most spectacular and important advances in knowledge have come through the recognition that two universes of discourse, formerly believed to be separate, are actually describable as one universe through the use of new conceptual tools. The recognition that electricity and magnetism constituted a single universe was one of the most important advances in the past few hundred years. The present hope that proof may be forthcoming that gravity and the electrical universes of discourse constitute a unity is of major significance.

Fragmentation and differentiation are necessary in the early steps of developing sciences, but the biological field is long overdue for a reorganization that will make manifest relationships that unquestionably exist but are not demonstrable with our present conceptualizations. Perhaps the new orientation will be based on the individual as an organizational unit rather than on generalizations dealing with limited segments of behavior. Perhaps the reorganization will result from the introduction of a new technique, such as biocybernetics, which compels consideration of biological problems in terms of a new universe of discourse.

A Word on Multi- Inter- Intradisciplinary Approaches

A variety of specialists from separate but related universes of discourse studying the same facts or the same group of patients can make a valuable contribution by sharply defining the limits of each field and clearly specifying the

"intruding" factors. For practical purposes, such as treating a patient or building a bridge, the close association of individuals in related universes is almost essential. Furthermore, close association may clarify the obvious identity of concepts or suggest methods of reorganization.

There is, however, a particularly great danger if the group of scientists is "high powered," since they then feel under an obligation to interrelate concepts; frequently a synthetic, nonexistent system emerges that results in confusion and a great waste of time and money. As presently constituted, the frame of reference of some of the universes of discourse are completely incompatible with those of others, and any relationship between them would be artificial.

A Final Note

As the wealth of the world increases, as information accumulates, and as the importance of biological science is increasingly recognized there is every expectation that (if we do not scuttle ourselves in the interim) we shall be able to explain, predict, and control human behavior. The moral and adjudicative values involved in who will do the describing, predicting and, particularly, the controlling are problems that must concern not only scientists but all of us in the immediate future. The prospect is unlimited but the responsibility is immense.

Summary

The ultimate goal of neurophysiology, psychophysiology, psychopharmacology, neurology, psychology, psychiatry and related disciplines is the explanation, prediction and control of human behavior. A serious problem arises in attempting to define how these various fields relate to one another. The relationship between any two events is determined by the question we are asking and the term "universe of discourse" refers to a group of events describable within a single frame of reference, of the same order, and rationally relatable to one another. At times the universe of discourse is incorrectly assumed to be known, at other times it is ambiguous, but for scientific purposes it must be either precisely stated or clearly inferable. Many of the ambiguities of bioscience arise from asking a question in one universe of discourse and seeking the answer in a quite different one. This leads to the formulation of the "Law of Answers": *we must answer a question in the same universe of discourse in which we ask it.*

There are points at which one universe of discourse intrudes into another and these, in turn, can cause methodological problems if the intruding event is ignored or if its effect is stated in terms of its own universe of discourse rather than the one into which it intrudes. This leads to the formulation of "The Law of Intrusion": *when an event intrudes from elsewhere its effect should be described in terms of the universe of discourse under study and not in respect to its primary universe.*

Much work in the biological field implicitly assumes the concept of the hierarchy of levels. Such a formulation is an arbitrary device that artificially limits both theory and practice. One universe of discourse is *not* reducible to another, as such a hierarchy presumes. Even within such a concept of "levels"

the level "above" is as necessary to understanding as the level "below." Nor does the fact that implementation of events in one universe of discourse involves activity in another demonstrate that the first is reducible to the second. In conclusion: there is no "fixed" paradigm for universes of discourse and the relationship of one universe to another depends on the question being asked.

An understanding of the relationship of one universe of discourse to another clarifies the meaning of environment. We can, therefore, state a "Law of Environmental Limitation": the environment (which includes certain events from other universes of discourse) must be sharply distinguished from the universe which it limits. This leads us to the role of the environment with the "Law of Environmental Support": *although the environment is necessary for support and maintenance of a universe of discourse, it should only be described if unusual or deviant.*

In the development of a scientific "proof" the following factors are contributory, but each is not sufficient of itself: explanation, regularity, replication, control, and/or prediction. The most useful single procedure to establish validity of a theory is its ability to provide a correct disjunctive prediction.

Another common confusion arises from the fact that to obtain information about a particular universe of discourse, the methods and techniques of a different universe of discourse must sometimes be utilized. This leads to the formulation of the "Law of Technique": *the technique used to obtain information does not necessarily determine the universe of discourse in which it is to be used.*

The factors governing description, explanation, and lawfulness are somewhat different when discussing a single universe of discourse or the relationship between two or more universes of discourse. One must seek identity of explanatory concepts, relationship between generalizations, and possible expansion and reorganization of events. A word on the abuse of multi-, inter-, and intradisciplinary approaches is raised.

Achievement of the ability to explain, predict, and control will not provide the value judgement or the standards to be used in carrying out such activity. It is the responsibility of the scientist to determine *how* this is to be done, but it is the responsibility of everyone to participate in decisions as to *what* is to be done.

The Appendix contains a philosophical discussion that relates existential reality to the derived conceptual model, and discusses the relationship between the two.

Reference

Pavlov, I. P. 1957. Experimental Psychology and Other Essays. Philosophical Library. New York, N. Y.

Appendix

A Philosophical Afterword

We continuously invent the past and then seek to explain it. Experientially only the present moment, the here and the now, can be truly said to exist. Certain thoughts we have labeled "This was once a here-and-now experience," whereas others bear the label "This may someday be a here-and-now experi-

ence." Both the once-were experiences and the may-be experiences are shadowy and unsubstantial compared to the here-and-now. To the one group we have given the label "past" and to the other "future," and we have found it convenient to invent something called time as a shorthand way of describing these experiences. Without ever having had a chance to consider whether they are logical or wise, we have attributed to time three characteristics that lead to some real dilemmas: (1) that time is unidirectional; (2) that it moves at a regular rate; and (3) that it is the same for everyone. Difficulties arise with unidirectionality because occasionally we feel, with certain experiences bearing the already-happened label, as though they were in the here-and-now, which upsets the order of things. To explain this reality away, we say that such events are dreams, hallucinations, or mystical experiences. In turn, the yet-to-come or will-happen feeling sometimes invades the present moment. Nevertheless it has become more important to preserve the integrity of "time" than to acknowledge reality. It has become "common-sense" to substitute a store-bought, ready-made universe for the disquieting uniqueness of actuality.

The idea that events as measured by a clock proceed at a constant rate is also a most perplexing one. Certainly our experience of the duration of certain occurrences or our feeling of how long ago they occurred does not agree with a clock or calendar. Again, if events were speeded up or slowed down (including the movement of all the clocks of the universe) we should have no way of knowing this "objectively." Finally, it is perfectly obvious that the experience of the duration of the same event differs greatly from one person to another, and even for the same person from one occasion to another. There are also a few minor idiosyncrasies, such as the fact that we cannot imagine time ever having had a beginning, nor can we imagine time having gone on forever. To a physicist the difference between lapsed time and biological time is so obvious that it does not even call for explication, and thus we find the explanatory concept we invented getting out of hand all on its own.

We have created similar dilemmas for ourselves by inventing space, and even more problems arise because of our belief in causal relatedness and our assumption of the complete lawfulness of nature.

However, functioning rigorously within this universe we have constructed, it becomes possible to make generalizations, the validity of which are checked by their ability to predict certain events, particularly those that do not recur on a regular basis. The cumulative description of events obtained by utilizing these presuppositions, checking by the same technique, and adhering to these rules makes up the body of what is known as science. It is for some of us an interesting way of dealing with the formal and abstract qualities of experience and—if one assumes the realities of time, space, and causal relatedness—a most useful technique for explaining the past, predicting the future, and manipulating the present. There is the danger that some people may substitute such a description of derived reality for experiential reality, but for the present purpose we shall operate in the frame of reference of "the game," that is, of science.

Accepting the conveniences of time and space, reality then becomes a cascading torrent rushing or eddying past in all directions as far as the mind's eye can see. In order for our limited comprehensions to deal with this flood we

seek certain regularities that are not too great for us to formulate and then relate them to other similar but different regularities. Up to the present our manner of doing this in the biological universe has been rather piecemeal. It is to be hoped that this paper will contribute to a clarification of the relationships between the various biological universes of discourse, which seems to be a prerequisite to an understanding of the nature of man.

DISCUSSION: PART III

Harry Grundfest (*Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, N. Y.*):* Like Marrazzi, I endorse heartily Zakusov's theoretical premise, cited above, "that the general patterns of the actions of particular pharmacological agents are the same, in their broad outlines, for the various divisions of the central nervous system . . . ." We also agree that the differences in the effects of drugs from one synaptic system to another "depend on the different sensitivities of synaptic formations and on the complexity of the organization of individual nervous structures."

The same premises, based on electrophysiological and pharmacological data obtained by studies on simple peripheral synaptic junctions, have prompted the formulation (TABLE 1) of a fairly general, but still only a rudimentary, electrophysiological theory of neuropharmacology (Grundfest, 1957*a*, 1958*a*, 1959). This theory has also been applied to the study of electrocortical physiology and pharmacology, recognizing "the complexity of individual nervous structures" of the neuraxial masses. The results have yielded a remarkably consistent framework for explaining and predicting the action of drugs on electrocortical potentials (Grundfest, 1958*b*, 1958*c*, 1960*a*; Purpura, 1958, 1959, 1960; Purpura and Grundfest, 1956, 1957; Purpura *et al.*, 1959*a*, 1959*b*, 1960*b*).

However, while Zakusov's statement that "the differences are only of a quantitative nature. . ." is also correct in many cases, it nevertheless requires some modification. It is true that a drug such as strychnine, which blocks inhibitory synapses with a very high degree of specificity (FIGURE 1), also inactivates the depolarizing activity of cerebellar synapses (FIGURE 2) when administered in high concentration, then acting as does *d*-tubocurarine (Purpura and Grundfest, 1956, 1957). Numerous other examples may also be cited of differential as opposed to absolute sensitivities, such as those of epinephrine and norepinephrine, or of *d*-tubocurarine and atropine. Nevertheless the extremes of these differentials may be so large as to present almost qualitative differences. This relative qualitative-quantitative selectivity occasionally rewards the search for drugs in which the qualitative aspect is dominant and that accordingly have relatively specific actions. The quantitative aspect, however, usually is manifested also, giving rise to the undesirable side effects that seem to accompany the "specific" actions of most synaptic drugs.

Nevertheless, distinctive and perhaps absolute qualitative differences do occur and must be stressed because of the theoretical importance of their existence. At the present time these pharmacological differences offer the most promising means for characterizing the molecular organization of different membranes (Grundfest, 1960*b*, 1961). For example, the electrophysiological properties of synaptic membranes of various invertebrate and vertebrate junctions are remarkably similar (Cerf *et al.*, 1959; Grundfest, 1957*b*, 1959; Grund-

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fest and Bennett, 1961; Grundfest *et al.*, 1959). This similarity indicates that the ionic mechanisms for developing electrogenesis are restricted in variety, a restriction that is consonant with the availability of but one depolarizing ion (Na^+) and of two repolarizing ions (K^+ and Cl^-) in the body fluids and cells.

TABLE 1
SYNAPTIC MODES OF ACTION OF DRUGS*

Type of synaptic drug	Type of synapse		Type compounds	Type effect
	Depolarizing	Hyper-polarizing		
Activators				
Nonselective	+	+	Acetylcholine norepinephrine	Excitatory or inhibitory
Selective (*a*)	+	0	Metrazol picrotoxin	Excitatory
(*b*)	0	+	?	Inhibitory
Inactivators				
Nonselective	+	+	*d*-Tubocurarine	Inhibitory
Selective (*a*)	+	0	GABA	Inhibitory
(*b*)	0	+	Strychnine	Excitatory

* Reproduced by permission from *Inhibition in the Nervous System and γ-Aminobutyric Acid* (Grundfest, 1960*a*).

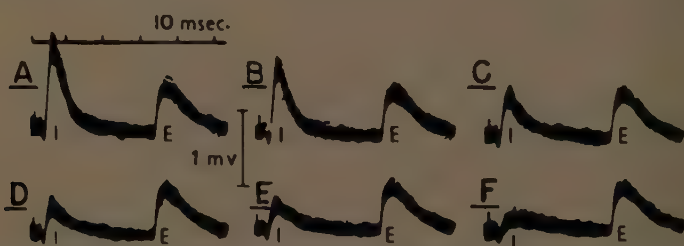

FIGURE 1. The membrane generating hyperpolarizing p.s.p.s maintains its pharmacological individuality, although the electrical response may be reversed and is then indistinguishable from that of a depolarizing p.s.p. Prior to taking this series of records, the hyperpolarizing p.s.p. evoked in the biceps-semitendinosus motoneuron by stimulating the quadriceps afferents was reversed by diffusing Cl^- from the electrode into the cell. This response (I) is shown at the beginning of each recording. Following it is a depolarizing p.s.p. (E), evoked by stimulating the afferents in the biceps-semitendinosus nerve. Strychnine salicylate (0.1 mg./kg.) was injected after *A*; it caused progressive diminution of I but no change of E during the next four 10-sec. intervals (*B* to *E*). The reversed hyperpolarizing p.s.p. almost disappeared after a second injection (*F*). Reproduced by permission from *The Physiology of Nerve Cells* (Eccles, 1957).

The pharmacological differences among synapses of the same electrophysiological species are vast (Grundfest, 1958*a*, 1959). They range from the absolute insensitivity of some invertebrate synaptic systems toward the familiar cholinomimetic and adrenomimetic agents to interesting inverted relations between pharmacological properties (TABLE 2). Even in the nearly related decapod Crustacea the effects of a given drug may be widely different (Florey and Hoyle, 1961; J. P. Reuben and H. Grundfest, unpublished data). These

data indicate that the membrane structures that have identical electrophysiological properties differ sharply in their chemical nature.

Differences in transmitters and in pharmacological properties of motoneurons and interneurons have been shown in the cat (cf. Eccles, 1957). Furthermore, not only do excitatory and inhibitory axosomatic synapses in the same cell differ pharmacologically, but axodendritic excitatory and inhibitory synapses differ from their respective asoxomatic counterparts (Grundfest, 1958*a*, 1958*b*,

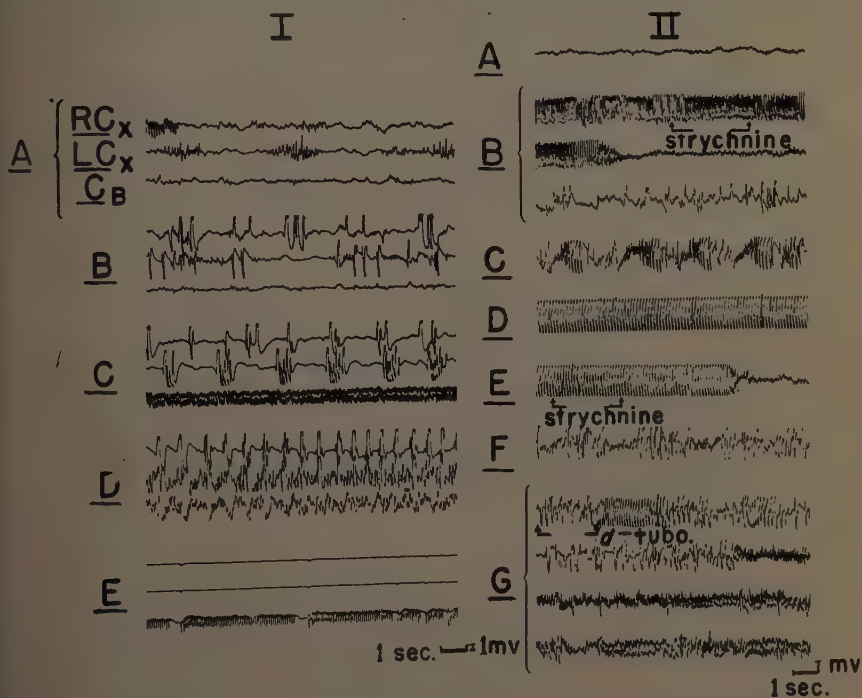

FIGURE 2. I: differential effects of the topical and systemic applications of strychnine to the cerebral and cerebellar cortex. *A* is the cortical record showing, from the top, the right and left cerebral cortexes and the cerebellar vermis. *B* shows the result of the topical application of 0.5 per cent strychnine to each of the three recording sites; it induced cerebral seizure but had no effect in the cerebellum. Three minutes after the intravenous introduction of 0.3 mg./kg. of strychnine (*C*), we see enhanced cerebral activity and cerebellar tetanus. A convulsive pattern at all three recording sites is seen (*D*) 2 min. after the intravenous administration of an additional 0.8 mg./kg. of strychnine. Two minutes after the intravenous administration of 3.0 mg./kg. of *d*-tubocurarine (*E*), there is cerebral quiescence and a return of cerebellar tetanus.

II: the different effects of a high concentration of strychnine on the cerebellar activity of a decerebrate cat. *A* is the surface activity from the anterior vermis after decerebration. *B* represents a continuous record beginning 50 sec. after the administration of 0.5 mg./kg. I. V. of strychnine. At the mark (*upper record*) 2.5 mg./kg. I. V. of strychnine led to temporary quiescence (*middle record*) and the return of activity (*lower record*). Fifteen minutes later (*C*) note the interruption of rapid cerebellar activity, probably by spinoreticular actions. *D* and *E* are a continuous record, 5 min. later. The further injection intravenously of 2.5 mg./kg. of strychnine again blocked activity, which returned (*F*) 8 min. later. *G* is a continuous recording 5 min. later. The injection of 3.0 mg./kg. of *d*-tubocurarine caused a cerebellar tetanic pattern, as seen in *B*, but at a lower amplitude. Reproduced by permission from *The Journal of Neurophysiology* (Purpura and Grundfest, 1957).

1958*c*, 1959; Purpura, 1959; Purpura *et al.*, 1959*a*). As a result, modifications may be produced by the ω-amino acids in the electrocortical activity due to dendrites without affecting the responses of axosomatic synapses (FIGURE 3). There is good reason to suppose, also, that in different neuraxial regions the apical and basilar dendritic synapses may exhibit different pharmacological properties. Thus profound pharmacological differences can be demonstrated in similarly electrogenic structures of different neuraxial sites in a single animal (Sigg and Grundfest, 1959; Purpura, 1959; Purpura and Grundfest, 1959), and in the course of development of a given synaptic organization (Purpura *et al.*, 1960*a*).

Many varieties of differences in pharmacological properties are beginning to be uncovered in the course of comparative studies, not only on various synaptic systems but on electrically excitable membrane as well. The diverse actions of procaine can serve as an example. This drug is a curarimimetic agent block-

TABLE 2
DOUBLY INVERTED PHARMACOLOGICAL RELATIONS OF LOBSTER NEUROMUSCULAR SYNAPSES AND OF CAT AXODENDRITIC CORTICAL SYNAPSES, WITH RESPECT TO ACTIVATOR AND INACTIVATOR DRUGS*

Animal	Drug type	Synapse type	
		Excitatory	Inhibitory
Lobster	Activator Inactivator	Carnitine ?	GABA Picrotoxin
Cat	Activator Inactivator	Picrotoxin GABA	? Carnitine

* Reproduced by permission from *The Journal of General Physiology* (Grundfest *et al.* 1959).

ing the vertebrate neuromuscular synapses (Castillo and Katz, 1957; Furukawa, 1957; Harvey, 1939), and the synapses of eel electroplaques (Altamirano *et al.*, 1955). However, like some other synapse inactivators (eserine and *d*-tubocurarine), procaine also affects the electrically excitable membrane of eel electroplaques. Instead of responding with all-or-nothing activity, the electroplaques now become gradedly responsive (Altamirano *et al.*, *op. cit.*). Procaine also produces graded responsiveness in squid giant axons (Grundfest *et al.*, 1954; Kao and Grundfest, 1955), and this action is probably associated with the depression of Na^+ and K^+ conductances of the axon (Shanes *et al.*, 1959; Taylor, 1959). Nevertheless the responses of arthropod muscle fibers, which normally are small graded potentials, become all-or-none spikes when the muscle fibers are treated with procaine (Belton and Grundfest, 1961; Reuben and Grundfest, 1960). This effect (FIGURE 4) is probably ascribable to a relatively greater inactivation by the drug of the K^+-conductance system of the electrically excitable membrane than of its Na^+-conductance mechanism. As is also the case for the synaptic membrane, the electrically excitable membranes of different decapod crustaceans exhibit marked pharmacological differences in their reaction to procaine (L. Girardier, J. P. Reuben, and H. Grundfest, unpublished

data). Furthermore procaine does not inactivate the synaptic membrane of the lobster at concentrations that markedly affect the responses of both the axons and of the electrically excitable membrane of the muscle fibers (H. Gainer, J. P. Reuben, and H. Grundfest, unpublished data).

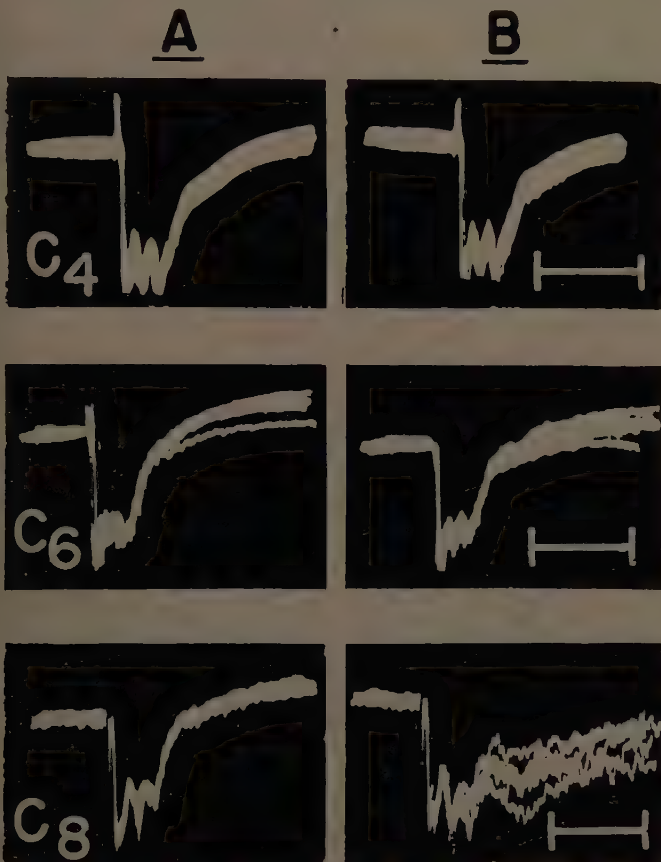

FIGURE 3. Pyramidal tract activity when the dendritic responses in the cerebra cortex are affected by ω-amino acids. Column A shows the discharge recorded from the pyramidal tracts to the stimulation of the cerebral cortex in cats, followed by the application of 0.3 cc. of 1 per cent ω-amino acid for 10 min. The substances were C_4, C_6, and C_8, as noted in each row of records. The responses of Column B were obtained when the cortical potentials had been altered. Despite these changes, the pyramidal tract responses, generated by direct electrical stimuli and by axosomatic synaptic excitations, were not affected (C_4, C_6) except when, as in the case of C_8, the drug caused convulsions. A long after discharge, associated with the convulsions, then developed. There are 10 superimposed traces in the upper records and 5 each in the middle and lower sets. Time calibration: 10 msec. Reproduced by permission from *The Journal of Neurochemistry* (Purpura *et al.*, 1959*b*).

The action of procaine on cat motoneurons appears largely to depress Na^+-conductance (Curtis and Phillis, 1960). Atropine is also said to have similar effects on the spinal neurons, but in crustacean muscle fibers its actions differ markedly from those of procaine (Girardier *et al.*, *op. cit.*). Analogous

pharmacological differences may account for the findings that a number of ω-amino acids that are synaptic agents on axodendritic synapses appear to act on the electrically excitable membrane of cat motoneurons (Curtis *et al.*, 1959). The motoneurons also respond to iontophoretic applications of many other agents that do not affect the axodendritic synapses (cf. Curtis and Watkins, 1960; Purpura *et al.*, 1959*b*).*

To summarize the foregoing: it is probably not too rash to say that every degree of complication that may be imagined by the physiologist has already arisen in the enormous number of cells and synaptic interconnections of the brain. Thus qualitative as well as quantitative differences must be stressed and sought in attempts to analyze the pharmacological behavior of the complex neural organizations and to utilize these analyses for enlarging our knowledge and control of brain activity (TABLE 1).

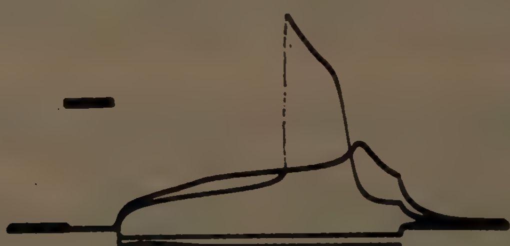

FIGURE 4. The enhancement of responsiveness in crayfish muscle fibers by procaine. Two records are superimposed; in each, one trace monitored an intracellularly applied depolarizing current, with the magnitude indicated by a downward deflection. The other simultaneously recorded trace is of the membrane potential. The larger current and the larger initial membrane potential were recorded from the fiber before applying procaine. The stimulus produced only a small, late response. A few seconds after applying 0.1 per cent procaine a smaller applied current evoked an all-or-none spike. The calibrating pulse at the beginning of the records represents 50 mv and 100 msec. From L. Girardier, J. P. Reuben and H. Grundfest, unpublished data.

I shall limit my comments on Marrazzi's paper to the portion that serves as the theoretical electrophysiological and pharmacological basis of his explanation of "behavioral patterns."

A number of electrophysiological laboratories have studied the transcallosal response (TCR) evoked at a site in one cerebral hemisphere by stimulating the opposite homologous region (cf. Purpura, 1959). In agreement with the anatomical complexity of the responding neuronal organization (Nauta, 1954), the TCR has a very complex electrophysiological composition that, thus far, has been only partially analyzed (Purpura and Girado, 1959; Purpura *et al.* 1960*b*). That analysis does not bear out Marrazzi's conclusions that the TCR is "a readily quantifiable functional 'unit', which is sufficiently simple and sufficiently representative of cerebral synapses in general to serve, so to speak.

* Some doubt may be raised regarding the use of the iontophoretic techniques on neurons in the spinal cord. Strychnine, whose actions are well established (Eccles, 1957; Kuno, 1957) does not block inhibitory synapses of motoneurons when it is applied iontophoretically (Curtis *et al.*, 1959), although injection of the drug into the spinal cord through a fine syringe produces its classic effects (Curtis, personal communication). Recent work by Kuno (1960) casts doubt on the previously published data using the ionophoretic technique.

as a building block for patterns. . . ." The TCR recorded from the suprasylvian gyrus "commences with a short latency spike presumably signaling antidromic and orthodromic axonal activity followed by slow surface positivity which reflects activation of deeper lying elements. . . . The surface positivity is terminated in surface negativity . . . (which . . . presumably represents a p.s.p. of apical dendrites" (Purpura, 1959, p. 124).

Even if all the activity recorded as the TCR were due solely to the response of the terminal neurons of a very simple circuit, it is no longer possible to regard the potentials as simple. Inhibitory as well as excitatory p.s.p.s might be involved in the cortical activity, and that factor of complexity must be taken into account to the extent that the TCR is composed of p.s.p.s. The TCR certainly includes axosomatic excitatory and inhibitory synaptic activity of corticospinal neurons, since an efferent discharge that can be modified by various experimental procedures is observed in the corticospinal tract (Purpura and Girado, 1959). In actuality, the TCR probably involves axodendritic and axosomatic synapses in several types of cortical neurons. Thus the electrical potentials recorded from the surface derive from a complex of generators arrayed in the depth of the cortex. Such complexity is clearly demonstrable (FIGURE 5) by examining the components of surface and depth recordings before and after application of a drug of rather simple action, γ-aminobutyric acid (GABA). This and other evidence (Purpura and Girado, 1959; Purpura *et al.*, 1960*b*) show that the influx of impulses into the cerebral hemisphere via the transcallosal fibers sets into motion a complex train of activity that is only dimly reflected in the TCR. The latter contains a large amount of surface positivity resulting from negative potentials in the cortical depth. However, much of this surface positivity is counterbalanced by a surface negativity that is generated superficially and that represents the net of positive and negative superficial activities.

Classical, simplistic pharmacology is reflected in Marrazzi's statement that there are only "two degrees of freedom possible to cell function in general and to neuronal function in particular, the increase and decrease that we recognize as excitation and inhibition." Both excitation and inhibition may be processes that involve "increase" in activity of a neuron by the excitation of appropriate synaptic membranes. Conversely, both "excitation" and "inhibition" may be caused by the blockade of activity initiated by a stimulus, as I noted in my discussion, above, of Magoun's paper.

In the realm of the manifestations of central nervous activity, whether as motor or electrocortical activities, even a simple survey of the possible modes of action of synaptic drugs (TABLE 1) demonstrates that overt "excitation" and "inhibition" can be produced by widely different means. Thus under certain conditions *d*-tubocurarine can produce convulsive activity (Feldberg, 1958; Purpura and Grundfest, 1957; Wright, 1955). In some circumstances it can evoke a cerebellar "tetanus" while eliminating cerebral cortical activity (FIGURE 2). Marrazzi at one point recognizes the possibility of some complexity by accepting what we have termed "inhibition of inhibition" (cf. Purpura & Grundfest, 1957; Grundfest; 1960*a*). Marrazzi describes it as a "release phenomenon" due to inhibition of an inhibitory tract that is in close relation to the final path.

Marrazzi's characterization of neurons as "bistable systems" probably do not imply that he regards them as bistable digital systems (cf. Grundfes 1958*b*). However his formulation does seem to imply that inhibition an excitation are antithetical and do not occur simultaneously in the same ce They certainly can do this in peripheral synaptic junctions, such as crustacea neuromuscular synapses, and they can do so also in spinal and cortical neuron of the cat. As Charles Sherrington stressed long ago (cf. Grundfest, 1960*a*

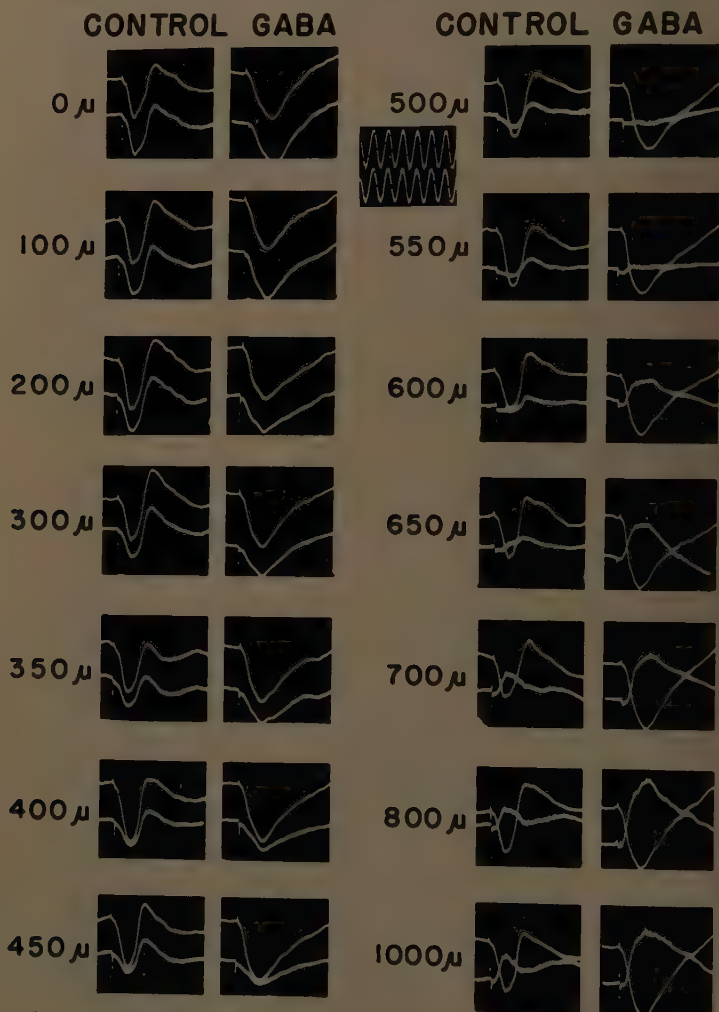

FIGURE 5. Simultaneous surface and depth recordings of the transcallosal response (TC before (*left*) and after (*right*) the topical application of γ-aminobutyric acid (GABA). T upper trace in each record is from an electrode on the surface; the lower trace was obtaine with an exploring microelectrode, situated first on the surface (0 μ) and then at various dept below the surface, indicated at the left of each set. The calibrations are 100 cps and 300 μ Reproduced by permission from *Electroencephalography and Clinical Neurophysiology* (Pu pura *et al.*, 1960*b*).

inhibition is an independent phenomena in the mammalian central nervous system, coequal with excitation.

Electrophysiological and pharmacological evidence on many systems of the brain demonstrates that both types of activity occur in the electrocortical records, including those of transcallosal responses. However since these activities are generated in the depth of the cortex as well as on its surface, a

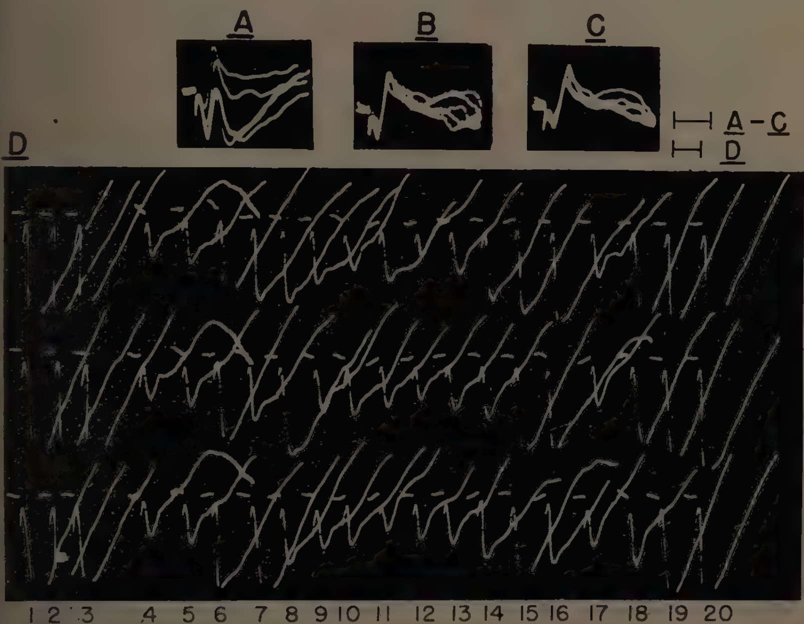

FIGURE 6. Changes in the transcallosal response (TCR) produced by brain stem stimulation before and after the response had been modified by GABA. *A* is the variable TCRs seen in five consecutive superimposed records, taken every 2 sec. *B* shows a similar sequence during brain stem stimulation at 200/sec. The stabilization of the TCR persisted, as shown (C) in 5 superimposed traces evoked in the interval 10 to 20 sec. after the end of the brain stem stimulation. *D* shows the effects of brain stem stimulation on intercurrent and subsequent TCRs after the latter had been modified by topical application of GABA. Each line shows 20 consecutive responses, evoked at 2-sec. intervals. Records 1, 2, and 3 are the responses before, and 4 and 5 are the responses during, the brain stem stimulation at 200/sec. The subsequent cyclic changes in the TCR are shown in records 6 to 20. The responses of the second and third sequences were repetitions to demonstrate the basic identity of the pattern of changes produced in the TCR after brain stem stimulation. Reproduced by permission from *Electroencephalography and Clinical Neurophysiology* (Purpura *et al.*, 1960*b*).

diminution of surface negativity, which Marrazzi regards as "inhibition," might be due to surface positivity caused by an augmentation of a deep negativity caused by excitatory p.s.p.s. The data on alteration of the TCR by GABA bear out this conclusion. Marrazzi regards GABA as an "inhibitory" agent. However, it augments the surface-positivity recorded in many types of responses (cf. Purpura *et al.*, 1959*a*, 1960*b*; Grundfest discussion, *loc. cit.*), including the TCR, as well as deep negativity of the latter (FIGURE 5). This finding is consistent with our interpretation (Purpura *et al.*, 1957*a*, 1959*b*) that

GABA is a selective blockader of depolarizing axodendritic synapses. Th elimination of the surface-generated negativity unmasks in the TCR the dee negativity that is normally counterbalanced by the former. After treatmen with GABA the TCR approaches the conditions of volume conductor recordin that are not met in the normal response (Purpura *et al.*, 1960*b*; Grundfes 1960*a*).

The TCR remains complex, however, even after it has been "stabilized" an "simplified" by application of GABA to the cortex (FIGURE 6). The TCR i this experiment was initially highly variable (*A*), but during *B* and for abou 1 min. (*C*) after stimulation of the reticular formation at 200/sec., the re sponse became stabilized into the simple pattern of positive-negative potential The response was also stabilized by GABA (*D*), but took on a different tempor aspect although it still could be described as a positive-negative sequence. 4-sec. stimulation of the brain stem at 200/sec. altered the TCR, tending t restore it to the form seen in *B* and *C*. At the end of the stimulation and fo nearly 1 min. thereafter the TCR underwent a regular sequence of change its positivity and negativity waxing and waning. These changes indicate tha the reticular activity had initiated a complex but patterned impingement modifying influences upon the neurons that are involved in the TCR. Th patterning probably resides in the cortical layers, since a similarly cyclic se quence of changes also occurs in the case of the superficial cortical respons or SCR (Purpura *et al.*, 1960*b*).

I regret that so experienced a pharmacologist as Marrazzi has not resorte to another class of pharmacological agents, the long-chain ω-amino aci (Purpura *et al.*, 1957*b*). We regard their general mode of action as the counte part of that of GABA, but blockading the axodendritic inhibitory synaps without affecting the excitatory. Such experiments in Marrazzi's behavior studies might be useful to test his analysis of the electrophysiological an pharmacological basis of behavioral patterns.

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V. V. ZAKUSOV: I have been asked: May we have some details of Kaveri and Pidevich's work, mentioned in my paper on the effects of analgesics an neuroplegics on coronary reflexes, and especially on the technique of elucid tion of the reflexes?

The coronary chemoreflex is elicited by the usual method: namely, the su stance that elicits the reflex, for instance, urethane or serotonin, is injected b means of a catheter inserted into the descending branch of the left corona artery or into the circulatory coronary artery.

We are studying the effects of many pharmacological substances on corona chemoreflexes. It is very interesting that their effect depends from cent representative. For instance, reserpine depressed the cardial chemorefle evoked by serotonin but not by veratrine while, at the same time, chlorprom zine depressed the reflex that evoked veratrine and serotonin.

I have noted with very great interest the remarks of Marrazzi, who has ou lined many useful concepts. I am glad that we share a common interest in th field, for this will certainly contribute to the solution of our problems.

I am very grateful for Kline's remarks on my paper, and I shall certain take them into account in further work.

I agree with Grundfest: I don't believe that different narcotics have identic action. I know that synaptic transmission is a very complex process and th narcotics could act on counterparts of this process, and I have data indicati that some pharmacological substances act on presynaptic membranes. I ho at some time to show that different narcotics do not have identical actions b do have some common principles in their actions.

NEAL E. MILLER (*Department of Psychology, Yale University, New Have Conn.*): Toward the end of his paper Marrazzi points out that drugs may useful in facilitating the extinction of bad habits and thereby may allow goo habits to be relearned. It happens that Herbert Barry III and I have pe formed an experiment on this problem. In our experiment we used an a

roach-avoidance conflict of the type theoretically analyzed and experimentally studied by Miller (1959).

First, hungry rats were trained in a Skinner box to press a bar that caused ood to be delivered as a reinforcement. After they had thoroughly learned his response, they received a series of traumatic electric shocks when they ouched the bar. Then the shocks were turned off. The animals continued o show conflict by avoiding the bar. This fear of the bar may be considered he "bad habit" that we desired to extinguish. Our problem was to reeducate he rats emotionally so that they would press the bar to get food.

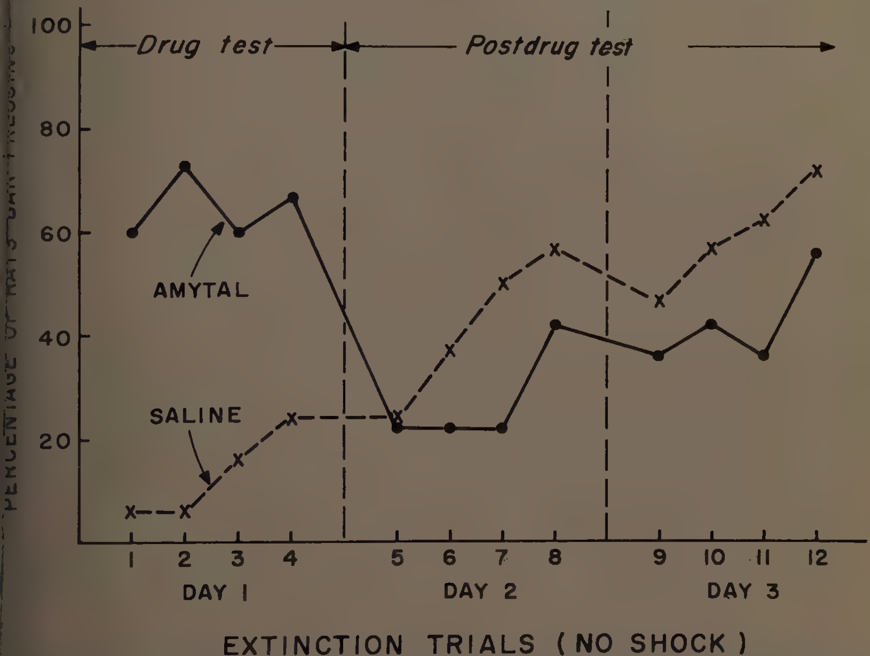

FIGURE 1. The therapeutic effects of sodium amytal failed to transfer from the drugged o the nondrugged condition. Reproduced by permission from *The American Psychologist* Miller, 1961).

In order to see whether the drug would help the animals to return to the bar, ve gave one half of them an intraperitoneal injection of amobarbitol sodium, ommonly called sodium amytal (20 mg./kg.) 15 min. before the rats were laced in the bar-pressing apparatus for four 40-sec. tests. The other half of he group received a control injection of isotonic saline.

The results are shown on the left side of FIGURE 1. During the drug test he animals with amytal pressed the bar much more frequently than those vith saline. However, as Dollard and Miller (1950) have pointed out in their earning-theory analysis of neurosis and psychotherapy, for such emotional ounter-conditioning to be effective it must generalize from the drugged to the ormal nondrugged condition. Therefore we gave all of the animals tests vithout the drug for the next 2 days. There was an enormous stimulus-gener-

alization decrement. The beneficial effects of practice with the drug clear did not generalize to the nondrug state. If anything, the rats that had r ceived their initial training with the drug were slightly inferior on the nondru test, but this last difference does not approach statistical reliability.

FIGURE 2 shows the results of an exactly similar experiment with an injecti of 2 mg./kg. of chlorpromazine. Although the fear-reducing effects of th drug on the very first trial are considerably less than those with sodium amyta there is much better generalization to the normal state. In this case, th

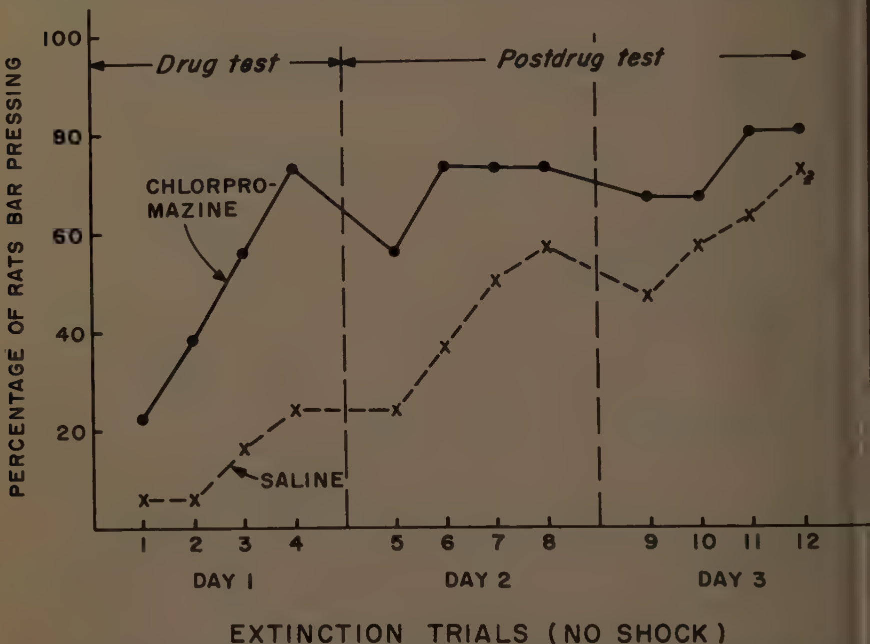

FIGURE 2. While chlorpromazine produces less initial improvement than does sodiu amytal, more of the gain seems to persist during subsequent tests without drugs. Reproduc by permission from *The American Psychologist* (Miller, 1961).

rats that extinguished their fear and relearned bar pressing with the aid the drug were superior to the control group in the postdrug test.

Comparing the two experiments, it may be seen that the drug that wa *inferior* in the type of testing most commonly used in screening drugs—namel testing for the immediate effects of the drug on performance—actually wa *superior* in the long-term therapeutic effect that generalized to the norm nondrug condition. A dose-response study strongly indicates that this diffe ence was a function of the type of drug used, rather than of the specific dos involved in this particular experiment. Since this dose-response study do not yet involve enough cases for high statistical reliability, this last conclusi must be accepted as only tentative.

I might speculate, however (I emphasize that this is speculation) that t difference among the barbiturate, sodium amytal, and the tranquilizer chlo

[ch]lorpromazine is due to the fact that the amytal produces a great involvement of [t]he reticular system while the chlorpromazine does not produce as much gen[e]ralized involvement of that second sensory pathway. In order to confirm [t]his hypothesis, one would find it necessary to study a whole series of drugs [t]o see how well the generality of the involvement of the reticular formation [c]orrelated with the transfer of training to a postdrug test.

I believe that all workers recognize the importance of such careful correla[t]ions between neurophysiological and behavioral effects. Before one can [m]ake such correlations meaningfully, one often needs a better understanding [o]f exactly what the behavioral effects really are; in many cases, there is need [f]or further analytical work at the purely behavioral level.

Barry and I are in the course of trying to perform analytical studies on drugs [t]hat are known to have interesting clinical effects. Some of the techniques we [h]ave developed for objectively studying the motivational effects of drugs are [d]escribed elsewhere (Miller and Barry, 1960).

Starting with sodium amytal, we have shown that this drug appears to reduce [t]he fear-motivated avoidance component of a conflict more than components [m]otivated by either hunger or thirst. In further experiments we have found [t]hat the foregoing result is not primarily due to a greater effect of the drug on [t]he more recently established habit of avoidance; we have secured similar [e]ffects when avoidance was the first-learned habit.

One experiment suggested that the fear-reducing effects of this drug in the [S]kinner box were not due merely to interference with the rat's ability to dis[c]riminate the tone used as a cue for danger in that situation. However, an[o]ther experiment in an alley showed that the drug either did interfere with [d]iscrimination or produced recovery from experimental extinction. Thus, [a]lthough a number of indirect modes of action have been ruled out, we have [n]ot yet decisively narrowed down this drug's fear-reducing effect to a direct [a]ction on the physiological mechanism for fear (Miller, 1961).

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K. F. KILLAM (*Department of Pharmacology, Stanford University, Palo Alto, [C]alif.*): I propose to present an illustration of a deviance produced by drugs [t]hat bears on the question of whether, as suggested by some of the contributors [t]o this monograph, the description of how a synapse or synaptic junctional [a]rea responds to a variety of induced stimuli will describe the functioning of [s]ynapses in general, the configurations of synapsing neurons, or the areas of [t]he central nervous system. The following information would suggest that [t]his generalization is not sufficient.

The illustration (FIGURE 1) is taken from some experiments E. Roy Joh and I carried out several years ago, and depicts the electroencephalograph recordings, from chronically implanted electrodes, of the responses of two ca to the presentation of flashing light. Both cats had received reserpine at μg./kg.; both exhibited the same classic pharmacological effects in that the showed miosis, motor depression, bradycardia, and diarrhea. The upper s of tracings is from the animal for whom the flashing light served as a condition stimulus, indicating that unless he crossed from one compartment to anoth within 15 sec. he would receive an electric shock to his feet. To the anim whose brain electrical activity is shown in the lower half of the illustration th flashing light was simply a peripheral stimulus pattern.

Data of this type indicate that, in comparable brain areas, the amount evoked electrical activity in the presence of reserpine differs, depending upo whether the stimulus has significance for the animal.

To us the data pose two questions: (1) What is the appropriate method approaching the mechanism of action of drugs affecting the central nervo system? (2) What may be postulated as the neurophysiological mechanis by which the responses of the two animals differ?

In consideration of the first question: since the central nervous system h as its monitory exchange the generation of behavior, it would seem most logic to me that one should study the responses of cells and cell populations in man areas in the central nervous system simultaneously while the animal is present a peripheral stimulus associated with the generation of a behavioral paradigm Without the use of a behavioral referant, the description of the mechanism drug action at any given synapse may be analogized to the checking of resisto or tubes in an amplifier without knowing whether the amplifier is functioni at its optimum.

Returning to the question of the mechanism underlying the differences be tween the responses in the two animals: the most obvious assumption is th since the signal, the flashing light, had a different meaning for each, the r sponses were different in the animals. This difference was accentuated by th use of reserpine. One might consider the possibility that reserpine has alter the functioning of the central core of the brain stem either to gate and sto or to gate and pass on information through the classic afferent pathways to th neocortex and to the rhinecephalon. However to date in our laboratories w have been unable to demonstrate that the administration of reserpine alters th functional state of the reticular formation. This contrasts with our observ tions following chlorpromazine administration, that is, of an increase in th negative feedback systems of the reticular formation on the classic affere systems. One need not, however, discard the reticular formation per se as th final common path for the regulation of afferent input. One might postula that rostral structures have a downstream regulatory effect upon the feedba systems of the reticular formation. These pathways would be corticifug from the neocortex, from the hypothalamus, or from rhinencephalic structure The final possibility, of course, is that, with the use of reserpine, mechanism totally different from those conceived thus far have been uncovered for regula ing afferent input into the central nervous system.

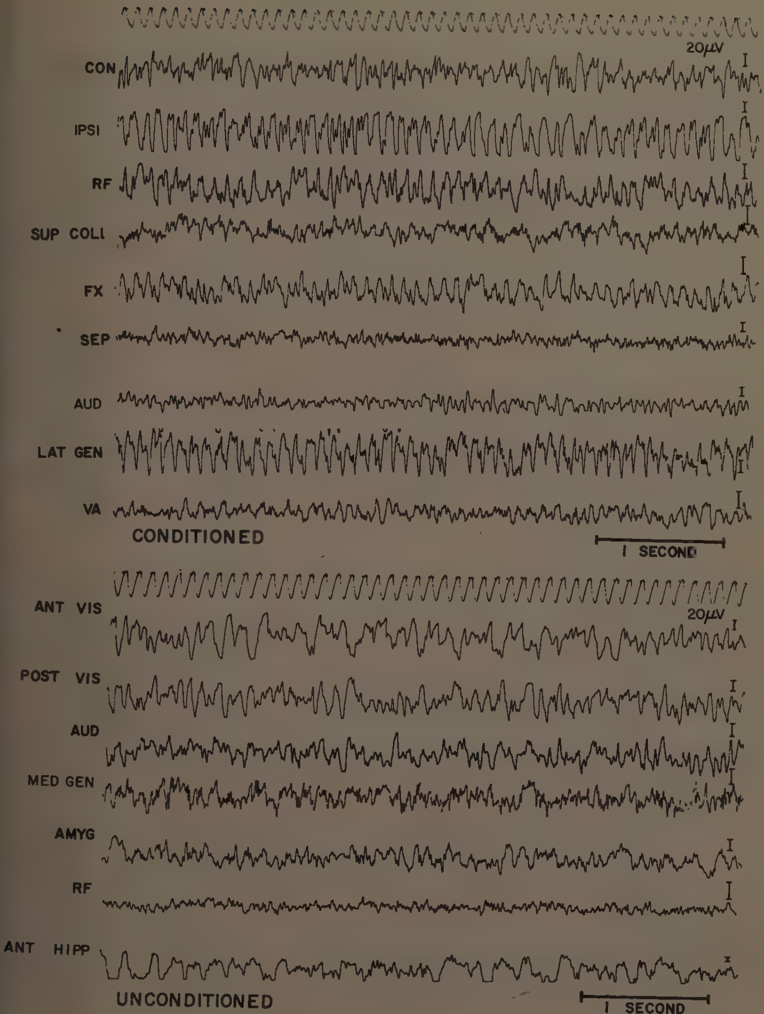


FIGURE 1. Comparison of the effect of reserpine on conditioned and unconditioned ani-
als. The electrical activity was evoked in response to the presentation of 10/sec. flashing
ghts in (*top*) an animal trained to perform a conditioned avoidance response to the stimulus
id (*bottom*) an unconditioned animal, following I. P. administration of 70 μg./kg. of reserpine
both animals. The records were made during the same interval following the administra-
on of reserpine.

Key: CON, bipolar derivation across midline between the two optic gyri; IPSI, bipolar
rivation from the same optic gyrus; RF, midbrain tegmentum; SUP COLL, superior col-
ulus; FX, fornix; SEP, septum; AUD, auditory cortex; LAT GEN, lateral geniculate nu-
eus; VA, nucleus ventralis anterior of the thalamus; ANT VIS, bipolar derivation from the
terior lateral gyrus; POST VIS, bipolar derivation from the posterior lateral gyrus; AMYG,
teral amygdaloid complex; and ANT HIPP, hippocampus.

Reproduced by permission from *Fifth Conference on Neuropharmacology*, 1960. H. A.
oramson, Ed. Josiah Macy, Jr. Foundation. : 162.

Amedeo S. Marrazzi: I was happy to have anticipated even for a momen Miller's very nice experiment, if only because it shows a convergence of thinkin

We might pursue the concept involved a little further and say that with ou orientation we should look for just that kind of difference between a generalize (Miller has used the term generalized) drug action such as amytal would have— with an over-all sedative action—and what we should ideally define as (an to some extent approach in tranquillizers) substances with selective blockin or depressant actions. The difference between effects on avoidance and o other conditioned phenomena such as alimentation (milk reward) were see

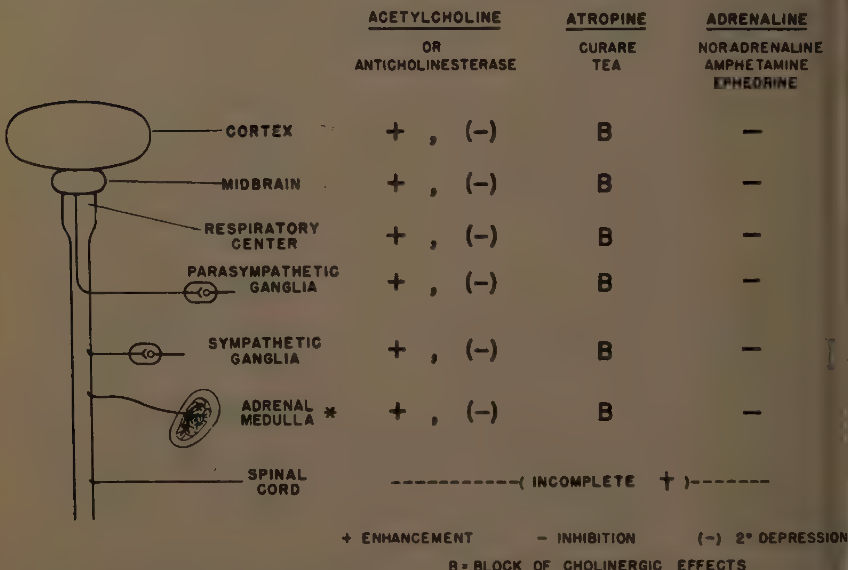


Figure 1. Similarity of cholinergic excitation and adrenergic inhibition at various syn apses. Key: + = enhancement; − = inhibition; (−) = 2° depression; and B = block cholinergic effects.

* The homologue of the sympathetic ganglion.

† Experiments are still in progress.

very clearly with chlorpromazine in our experiments. In addition, the avoic ance is now no longer reinforced with shock; thus we can interpret that particu lar avoidance as a maladaptive phenomenon that chlorpromazine is eliminatin at the same time that it is not eliminating the milk-rewarded condition phenomenon.

Turning to another subject: I am delighted with the growing pharmacologic awareness and sophistication that Grundfest manifests. Actually a good de of what he said is a detailed explanation of figure 5 in my paper, which showe that we had not neglected actions on the membrane. In the right-hand portio of the figure was shown a response metabolism. Study of such a diagra indicates that an inhibition can be achieved by activating an inhibitory recept or by blocking an excitatory receptor; excitation can be attained by the invers

operation of these two mechanisms. Which particular mechanism operates remains to be determined by specific experiments.

FIGURE 1 demonstrates why we like to entertain the hypothesis that there is a qualitative identity with only quantitative differences. Grundfest referred to something that he said four years ago; we can therefore refer to this old illustration, which shows, just as he has said, that there is a resemblance, a family resemblance, between central and peripheral synapses. My colleagues and I began our work in the field of peripheral synapses, and this figure is a tabulation of our results.

It is obvious that a true and authenticated exception causes any hypothesis to fall. We have not met that exception as yet; when we do, we shall change or modify the hypothesis.

As to whether there is any justification for thinking of acetylcholine and similar substances as neurohumoral central cerebral excitors, and of adrenaline, noradrenaline, serotonin and, incidentally, histamine as inhibitors: a good many years ago Chang and Gaddum laid down the postulates. The first thing that one would like to see in demonstration of these characteristics is the execution of a tremendous physiological artifact, that is, if products are liberated, the collection of these substances.

This may be done by creating a tremendous excess through maximal activation and by preventing destruction of the substance. This is relatively easy to do or not easy at all, depending on the site. It is easy to do in autonomic ganglia that can be isolated, but it is obviously very difficult to do in the brain.

There are other factors to be considered: the introduction of minute amounts of the candidate neurohumoral substance to test the reproduction of the phenomena under study, the local preservation of the substance, and the characteristic blocking of the substances by compounds known to have such an action.

We can certainly fulfill some of these postulates very well. One μg. of acetylcholine reproduces the phenomenon under discussion, and diisopropyl fluorophosphate, by preserving acetylcholine *in situ* will reproduce any number of anticholinesterases.

Ten μg. of adrenaline or 1 μg. of serotonin will produce inhibition (of the same degree). These are substances that are naturally found. We can accumulate them *in situ*, and FIGURE 2 shows some preliminary data that refer to serotonin.

What we have done is to take the lazy man's way out. If we cannot collect the substance, we can try to preserve it *in situ* by an inhibitor of the enzymes that would naturally destroy the substance; and that is what we have shown in the figure. On the left (*a*) is isopropyl nicotinic acid or iproniazid; on the right (*b*) is phenylisopropylhydrazine or JB-516. The top curves are the actual concentrations developed in the brain when these substances (approximately 0 μg.) are injected intracarotidly in the lightly anesthetized cat. The same thing can be done in the curarized cat. What should happen? The monoamine oxidase titer should decrease, should be inhibited, and that is the second curve in both cases.

As a consequence the serotonin should increase, and that is the third curve in both groups. If this phenomenon has anything to do with transmission the

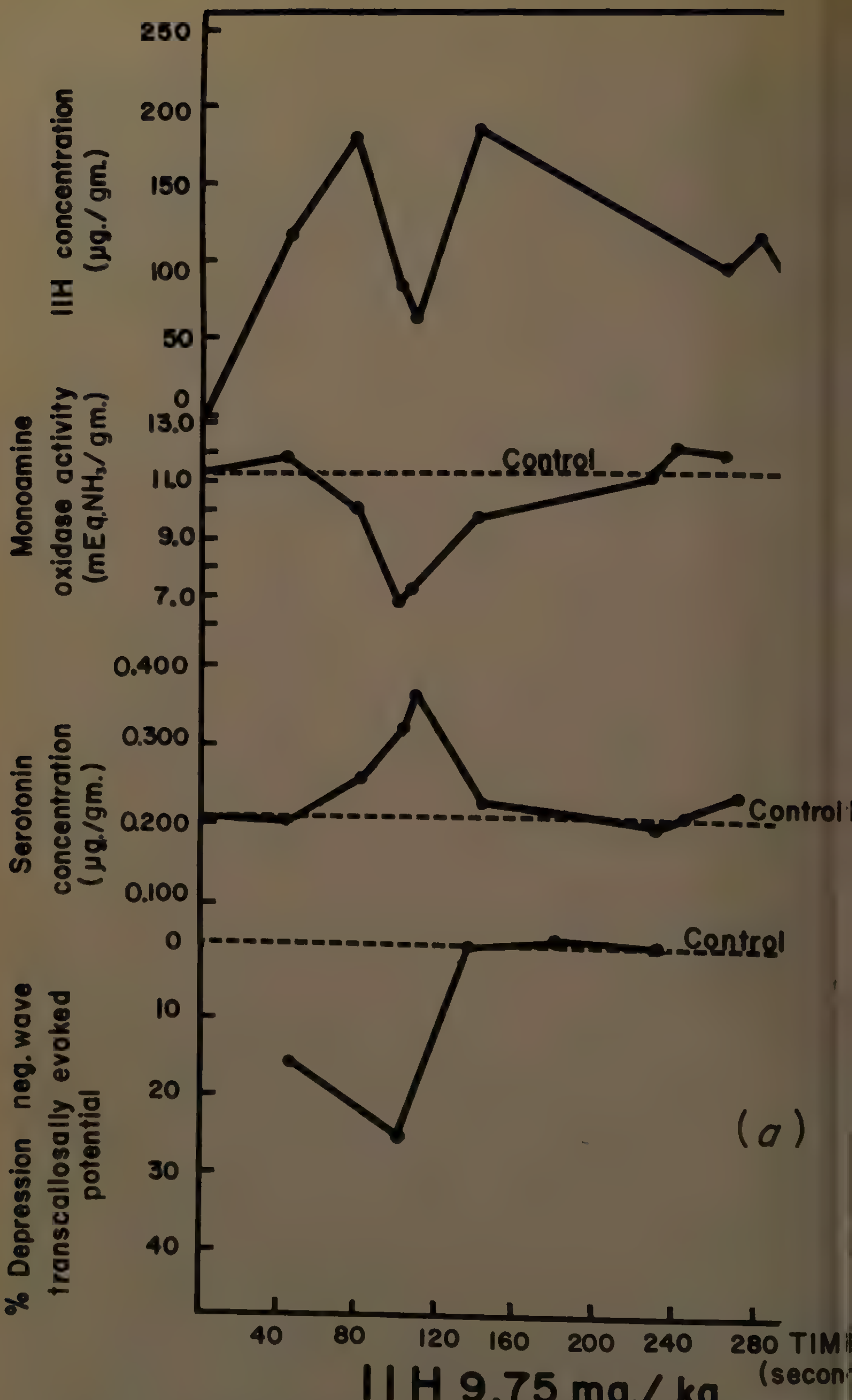
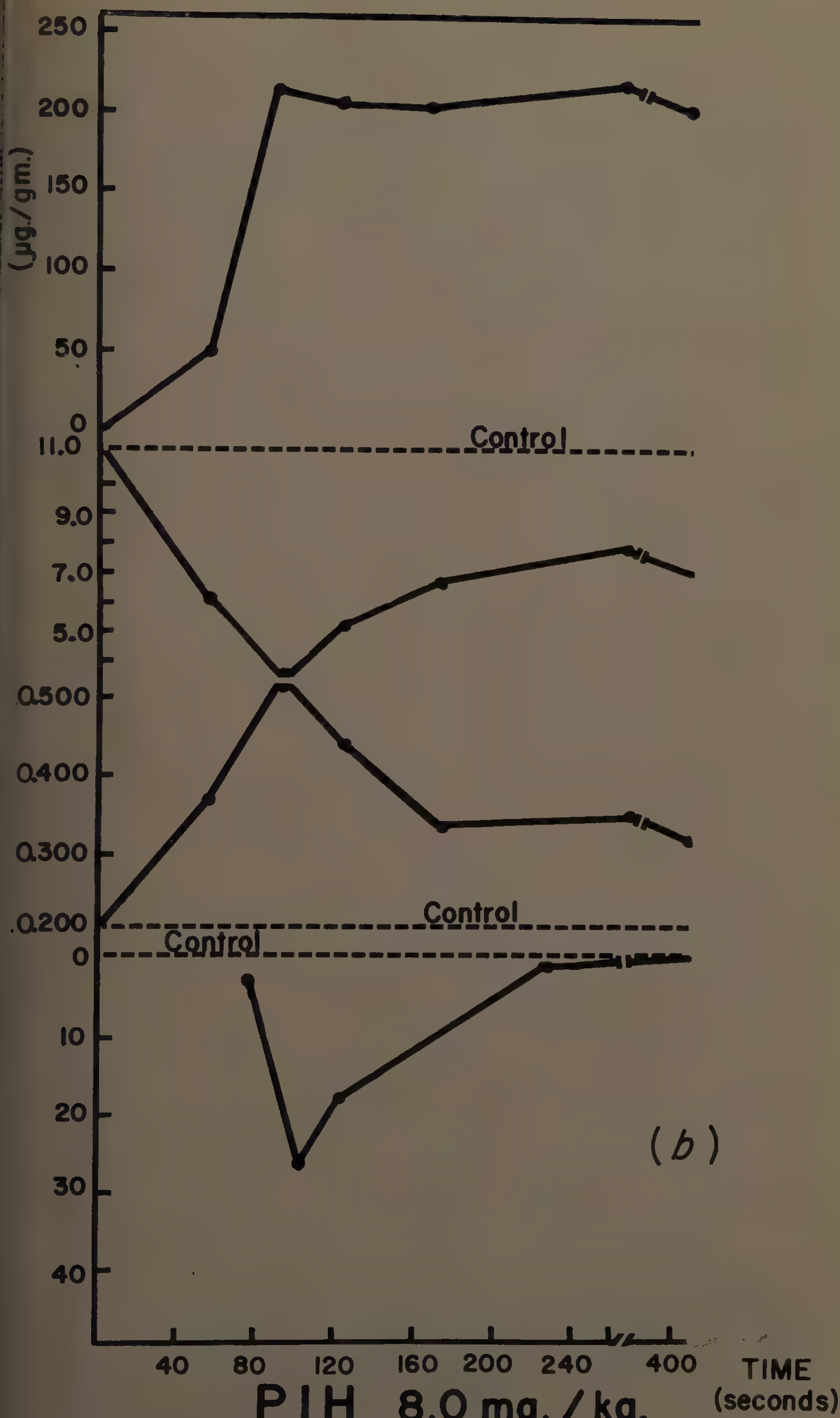


FIGURE 2. Correlation of biochemical and functional data at the cerebral synapses. T
chemistry and evoked potentials were from the ipsilateral hemisphere. See text.



noamine oxidase inhibitors were by administered intracarotid injection in the cat, and

index of output from the terminal synapse in the chain that we are talki
about should go down; here the height of the surface negative potential do
go down correspondingly in both cases.

I believe we are on pretty sound, if not absolute, ground in saying that
fulfill a major number of postulates. There is exquisite sensitivity to the
substances that have been demonstrated to be present. They can be preserve
They reproduce the action.

Study of the text of my paper will reveal that I carefully said "recordi
from the terminal synapse in the chain." We are not in a position to sho
exactly how many neurons are in that chain, although we still believe that
is a simpler chain, compared to the others under discussion.

May I conclude by citing his most inspiring and prophetic lines, written
1923: "Let the mind rise from victory to victory over surrounding natur
Let it conquer for human life and activity not only the surface of the ear
but all that lies between the depth of the seas and the outer limits of the a
mosphere. Let it command for its service prodigious energy to flow from o
part of the universe to the other. Let it annihilate space for the transferen
of its thoughts. Yet the same creature, led by dark powers to wars an
revolutions and their horrors, produces for itself incalculable material loss
and inexpressible pain and reverts to bestial conditions. Only science, exa
science about human nature itself and the most sincere approach to it by a
of the omnipotent scientific method, will deliver man from his present gloo
and will purge him from his present shame in the sphere of interhuman rel
tions."

HEINZ E. LEHMANN (*Verdun Protestant Hospital, Verdun, Que., Canada*
I propose to offer to you my thoughts on what I consider to be the reason an
the meaning for Nathan S. Kline's presentation in these pages, a philosophic
discussion in a meeting on Pavlovian science. Some may wonder how
fits in here; a historical approach may help us to see it more clearly in i
proper perspective.

There is a dialectical progression that seems to be invariable for science, f
each science, in its historical development. As I see it, each science go
through three different stages of development:

The first stage is one of instrumentation, in which the need and the preo
cupation with the development of instruments to observe, to measure, and
record is all-absorbing. We saw this hundreds of years ago when the telesco
was invented, followed by the microscope, the spectroscope and, much lat
the Pavlovian frame and the implanted cerebral electrodes. Each time anoth
instrument had been perfected, a great deal was written and said about th
new experimental device. Now this is happening again, on another level, wi
radiotelescopes, electron microscopes, infrared spectroscopes, microelectrod
and the highly complex instrumentation that allows us to record condition
behavior and the autonomic reactions of an animal at a distance. Much
our research energy is continuously going into instrumentation.

The second stage is one of development in each science: the stage of speci
methodology and experimental design. In the biological sciences we seem

be chiefly in this stage at the present time. Our instrumentation has been quite well developed. I think we have not yet reached ultimate development of it, but we are already busily engaged in the shaping of experimental designs and in the building of our methodology. We must consider what role statistics are playing: What are we going to do with the tremendous amount of data we are gathering? We are preoccupied with the processing of information, with computer techniques. All this is now very much in the spotlight of our scientific attention.

The third stage is one in which each science enters its last and most mature phase of development, one concerned with the philosophical analysis of where it belongs in the scheme of things.

For instance, around the turn of the century Albert A. Michelson performed his classic experiment on the speed of light, the results of which were extremely puzzling; nobody could explain them. Research was at that time at the end of the second stage. It had developed beautiful instrumentation. There was no better instrument that could be made to measure the speed of light than the one Michelson had at his disposal: he had a perfect experimental design, there was no better way of performing his task; yet he arrived at the incomprehensible conclusion that light moved at the same speed whether it was measured in the direction in which the earth was moving or in the opposite direction. Of course, there should have been a measurable difference of speed.

At that point, the third stage had to be entered, the stage of taking a hard philosophical look at what was going on. Albert Einstein was able to do it and, in so doing, he took time out of the universe of discourse in which it did not belong and put it where it did belong. Until then, until the turn of the century, we had treated time as though it was actually what our model, our analogue of it, was, namely clocked time. Time was something that a clock would measure.

This was a beautiful operational definition, but it did not work any longer. It had served very well until then, but at that stage of the development of the physical sciences, it had outlasted its usefulness and we had to look at what time *really* was or, rather, at what it was *not*. Only a philosophical analysis and revision could show us that the model was not the thing.

In the biological sciences, particularly in the behavioral sciences, we are now close to this point. We treat conditioned behavior as though it *is* normal behavior. We treat an experimental neurosis as though it *is* a real neurosis. We are not altogether at the stage where the physical sciences were at the turn of the century. Our instrumentation and our methodology is not as perfected as it was at that time in physics, so that we probably cannot yet commit ourselves entirely to the third stage. But it is a good sign for a science when it approaches this stage. The behavioral sciences are doing this now.

We have seen in this monograph several references to the marriage or fusion of neurophysiology and conditioning. We are concerned with psychopharmacology. How do psychology and pharmacology fit together? What is the relationship of conditioning to psychology? Of psychology to psychiatry? Of psychiatry to the best way of maintaining mental health? We need a philosophical look, and a very hard one, at what we are doing.

The first two stages, concerned with instrumentation and with methodology, require technicians in the first stage and scientists in the second, and much money for both; in the third stage, however, we require primarily philosophically trained minds. Einstein happened to be a physicist capable of highly competent philosophical analysis, which explains why he could get through the impasse that Michelson had not been able to overcome.

It is interesting that technicians and scientists are rather time-bound. For instance, if Galilei and a modern astronomer, or Newton and a modern physicist, were to meet for, let us say, a television interview, Galilei and Newton probably would require several month's briefing before they could carry on confidently in such an interview. However, let us assume that Bertrand Russell, who is living now, and Kant and Plato, who have been dead for considerable time, would meet to carry out such an interview. After one half hour of briefing they could probably communicate very well and meaningfully, because a philosophical analysis is a rather timeless undertaking.

Kline used the Socratic method of asking questions. Socrates often referred to his own function as that of a midwife. He said he was just helping the truth to be born by asking the questions. While I do not think that the birth of a new understanding of the behavioral sciences will be an easy one—we are only at the very beginning of it—I think Kline has rendered very able obstetrical service at this early stage of labor. Let us hope we shall all live to see, eventually, a healthy baby born.

O. V. Kerbikov: The subjects dealt with in the paper submitted by Kline are of tremendous interest to all psychiatrists, namely, those subjects associated with psychopharmacology.

As has been rightly pointed out, we are now entering a new period in which all psychiatrists tend to become pharmacologists and all the pharmacologists have almost become psychiatrists. As pointed out by Kline, also correctly, it is necessary to find in this field a common ground: one properly described by Kline as the universal discourse.

Kline said that he began his study by studying philosophy. May I remind you of the existence of the philosophical treatise called *Levyothan*[1] and, in this connection, point out how right we are to stress the need for one unified concept of the content of understanding in this particular field.

Kline has correctly stressed that it is necessary to explain a variety of facts and he also pointed out that many theoreticians suffer from the defect that they wish to explain everything. Here I must agree with him. It is often too early to give an explanation, and it is often better to wait until there are new facts available in order to avoid mistakes.

Therefore, may I emphasize my agreement with his point that we very often have to await new facts before we can jump to conclusions. However, the universal need or urge to explain everything is shared by all, and the feeling is especially strong among psychiatrists.

In this connection it may be said that psychoanalysis often explains facts that have not yet been discovered. Psychoanalysis is the mother Levyothan

of psychiatry. It is a great danger to psychiatry. Psychopharmacology is a complex of facts and, as such, represents the greatest threat to psychoanalysis. Psychopharmacology, a new field of knowledge, shows how unconvincing are the character and the premises of psychoanalysis.

May I in conclusion once again express my full agreement with Kline's statement that we need a fully common ground for scientific concepts and their understanding.

I shall read his paper at leisure in the hope and with the conviction that it will give me many new interesting facts that will be of great use to me in my future work.

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ZIGMOND M. LEBENSOHN (*Georgetown University, Washington, D. C.*): I submit the following quotations to indicate that Freud's orientation did take into consideration the organic point of view:

"It should be borne in mind that all our tentative psychological formulations (*psychologische Vorlaufigheiten*) will have ultimately to be grounded in the organic" (Freud, 1914).

"The edifice of psychoanalytic doctrine which we have erected is in reality but a super-structure which will have to be set on its organic foundation at some time or other, but this foundation is still unknown to us" (Freud, 1935).

"The shortcomings of our description would probably disappear if for the psychological terms we could already substitute physiological or chemical ones" (Freud, 1922).

"From a clinical standpoint the neuroses must necessarily be put alongside the intoxications and such disorders as Graves' disease. These are conditions arising from an excess or a relative lack of certain highly active substances, whether produced inside the body or introduced into it from outside—in short, they are disturbances of the chemistry of the body, toxic conditions. If someone succeeded in isolating and demonstrating the hypothetical substance or substances concerned in neuroses, he would have no need to worry about opposition from the medical profession. For the present, however, no such avenue of approach to the problem is (yet)* open" (Freud, 1925).

"The future may teach us how to exercise a direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind" (Freud, 1949).

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* Editors note: appears in German original but not in this translation.

Louis Lasagna (*Johns Hopkins University Medical School, Baltimore, Md.*). Nathan S. Kline has raised many important points in his paper. He has emphasized, for example, the need for asking the right questions. In the early part of his paper, questions such as "What is the basis of seizures?" or "What is the basis of delusions of grandeur?" are vague, ill-defined, and suggest no immediate experimental approach. By contrast, many of his later questions are perfectly good: specific, well-defined, and giving a reasonably unambiguous notion of what the questioner had in mind and what might be done to arrive at a solution to the question. Kline might therefore have added to his various laws one of the oldest laws of all: "Ask foolish questions and you get foolish answers." To this might be added a corollary: "Don't bother to answer questions that are trivial or are inadequately phrased."

Although I cannot agree completely with the various hierarchies outlined in his paper, I see eye-to-eye with Kline on the dangers of the Reductive (or "Nothing-but") Fallacy. I do not like, for example, the statement that "sociology is really nothing but group psychology." Or perhaps what I should say is that I do not understand what the statement means, but if I *did* understand, I probably should not like it. This section of Kline's paper reminded me all too vividly of a conversation held some years ago with a young neurophysiologist who informed me that those of us who were trying to approach the problem of behavior from the pharmacological, psychological, or any point of view other than the neurophysiological would be wise to step aside for a century or so until the neurophysiologists traced all the sources and sinks of the central nervous system; by that time we should fully understand what "mind" was. I regretfully told my friend that I could not afford to wait a century and, furthermore, that I was not sure that his particular scientific horse was the one on which I should put all my money. It seems unlikely that the answers to all of our problems will come from any single approach.

I should like to take issue with Kline's Law of Environmental Support, according to which the environment "need only be described if unusual, deviant, or of special relevance." Unfortunately, it is not always easy to know when the environment is "relevant." A good example of this would be the observations described by M. R. A. Chance some years ago[1,2] and recently reintroduced to American pharmacology by our group.[3] I refer to the interaction of aggregation and the toxicity of sympathomimetic amines. If amphetamine is given to mice grouped together, it is a much more toxic drug than when it is given to mice housed individually. Chance was originally led to his experiments by the great discrepancies in the results reported from different laboratories on the toxicity of amphetamine. It seems likely, in view of his research, that much of the discrepancy could be explained by differences in aggregation. However today one still finds that many drugs are being studied, including central nervous system stimulants, without much cognizance of the possibility for important interactions between the drug and numbers of animals per container. It is obviously impossible to list dozens of environmental variables in presenting one's data, but it is now well known that such factors as age, sex, and time of day can have important effects on drug responses; for scientists to continue to report experiments without specifying the basic conditions of these experiments seems highly capricious.

Kline reminds us of the importance of Occam's razor, or the law of parsimony. Certainly this law has a great deal of appeal, although if one looks at the historical attitudes toward Occam's razor one is not very reassured about its application. At various times in history, the law of parsimony has been viewed as God's will, or an excuse for laziness, or as an esthetic principle. None of these, I submit, is very encouraging as a scientific basis for its utilization. Furthermore, although clinicians utilize the law every day of their lives in trying to come up with a single diagnosis that will cover all of a patient's signs and symptoms, it is well known that the law of parsimony is very likely to be misleading in certain groups of patients, such as the aged, in which each patient usually has more than one disease. Accordingly, one ought perhaps to stress not only the need for parsimony in one's assumptions, but also the importance of seeking explanations that are most appropriate, whether they are simple or complex.

Kline reminds us of the traps of semantics, although I believe he has himself fallen into one in his use of the word "excitation." He states that our comprehension would be greatly aided "if a drug would cause 'excitation' . . . in both the electrophysiological and the psychological universes of discourse. . . ." Unfortunately, I think the word "excitation" is such a muddy one that it has little precise meaning, particularly in the psychological sphere.

We are living in paradoxical times. At the moment that science is uncovering more bits of data than ever before, we are seeing increasing difficulty in the communication of such data and, perhaps more important, in the integration of such data. It is not popular to be a Renaissance figure today, not only because it is considerably more difficult than in earlier times to encompass wide areas of human endeavor, but also because one is apt to be considered either a messenger boy running between disciplines, or a dilettante. Nevertheless I am convinced that we badly need more scientists who will attempt to integrate our information, and who will remind us of this by pointing out that we must periodically submit the logical and philosophical implications of our experimental approaches to an "agonizing reappraisal," and for this we are in Kline's debt.

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Nathan S. Kline (*Rockland State Hospital, Orangeburg, N. Y.*): I have difficulty, as usual, in rebutting or even remarking on Lehmann's comments because, unfortunately for the sake of argument, we usually agree. I should certainly have no objection to his analysis of the stages of science and I am grateful for his remarks.

As for Kerbikov, unfortunately he has not yet had time to read my paper and I think, in view of his own remarks, he surely will be very surprised by

some of the contents when he does read it: certainly in one sense we are looking for a common ground between the disciplines, but the great danger is to think that we are on a common ground when in point of fact we are not.

There is a school of approach (I am not certain that Kerbikov belongs to it) that says "let us find the facts and the theories will all take care of themselves," or "the facts will speak for themselves." If facts are given an opportunity to speak for themselves without any kind of organization, they usually speak in a meaningless word salad.

A book title by Henry Osborn Taylor should be memorialized; the book is called *Fact—The Romance of Mind*, and Taylor rightly makes the point that no fact can exist outside a theoretical framework. Facts are only concretions in a larger conceptual system; they do not exist aside from a theory. It is much better to know that you are utilizing a theory and have some sophistication and some critical attitude toward the theory rather than to think you are finding some pure and unadulterated "fact" that will correlate with something else and "explain all."

Kerbikov comments that psychoanalysis explains facts that have not yet been discovered. I quote my eminent colleague Victor Borge, who states that his uncle spent 20 years in the laboratory and emerged with the pharmaceutical cure for a disease that did not exist. Thus the crime is committed not only by psychiatrists and psychologists but equally by the psychopharmacologist and the chemist.

However, this elaboration of theories is the essence of science; to be able to predict the existence of the planet Mercury or of a disease that has not been identified, and then to go out and discover that there is such a planet or such a disease adds as much verification as one can give to a theory. Thus an explanation of facts "that don't exist" may actually lead to their discovery.

For those who know Lasagna, his commentary was most startling: it was oleaceous, sweet, almost out of character. He saved himself in the end by becoming somewhat more critical.

As Lasagna, I am sure, is aware, the bad questions at the beginning and the good questions in the end were specifically labeled as such and are there with malice aforethought to provide examples.

Lasagna again emphasizes that one should not attempt to answer trivial or meaningless questions. The great difficulty, of course, is how to know if they are trivial or meaningless. This again requires that we work within a theoretical framework, because if one asks something completely meaningless—for example: Is the moon happy?—it is a completely meaningless question because of the assumption of a whole universe of discourse about the moon, of which happiness could not possibly be a quality. Very often we know intuitively, or viscerally, if you will, that these are meaningless questions. However there are all kinds of borderline questions to which one's guts do not react as strongly as they should. If one has received sufficient conditional stimuli, perhaps by setting up a knowledge of the framework in which one is working, this reaction will occur.

Finally, in respect to the environment, I should like to agree with Lasagna that the word "excitation" is an excellent example of the poor use of a concept; this was not intentional on my part. This has saved Lasagna's reputation

since he did manage to find something wherein I had grievously sinned. *Mea culpa.*

I have the further pleasure of disagreement on another score, because I should still insist that the environment need not be described unless it is relevant. Lasagna urges that the environment be described, and uses as a model the experiments of Chance, in which the death rate was much higher in mice who were grouped together and then given amphetamines than in mice that were given amphetamines and kept in isolation. This is an excellent example in which the environment is relevant and, certainly, one should look for these things. However, had the death rate been the same for the two groups of mice, it would have been pointless to have described any special feature of the environment, because one would have had to itemize the entire universe of universes to describe all the things that might have relevance. Serendipity is the ability to pick up relevances that others do not recognize.

Lasagna's choice of example was excellent for another reason. Some people have argued that the reason that the mice died is that when one mouse started running around it started the other mice running, and it was the social behavior of the mice, their excitement, their juxtaposition, their social relationships, their psychological reactions to their social relationships and the physiological concomitants of their psychological reactions to their social relationships that killed them.

On the other hand (I am not an authority on this), I have also heard it said that the mice (which I believe were in a closed container) when given the amphetamines showed such increased activity that their temperatures went up to a point that made the drug lethal. This is an entirely different universe of discourse. On the basis of the death of these animals there is thus beautiful speculation about both neurophysiological and sociopharmacological behavior.

Certainly one must answer the question: To which universe of discourse does this particular phenomenon belong? By asking this question one can avoid a good deal of useless speculation. Either one group is wrong or the other is wrong; if it were known in which universe of discourse either group was talking, much trouble would thus be saved.

LASAGNA: In reply to Kline's comments I should like merely to point out that, in our initial paper on this phenomenon, we did not comment on the possibility that temperature might have been an important determinant in response for the simple reason that our data on this point were not very good. We were very much aware of the possibility, however, and we took scrupulous care to describe in detail the canisters employed so that anyone trying to repeat the experiment would *not* assume that our containers were anything but metal canisters. We went on to do (and to publish) much work on the importance of temperature in this phenomenon,[1] and we can assure Kline that the increased toxicity of amphetamine in the aggregated situation is not solely a matter of temperature changes although, as he has pointed out, amphetamine toxicity is certainly affected by temperature.

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Part IV. Irradiation and Generalization

SOME NORMAL AND PATHOLOGICAL PROPERTIES OF NERVOUS PROCESSES IN THE BRAIN

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Suppose it were possible to insert microelectrodes into all the nerve cells of the brain without injuring them or altering their normal condition, and to record their resting potentials and action potentials. Could we then, on the basis of our recordings, obtain a picture of the activity of the brain as a whole and relate it to the outward behavior of the animal? Could we say what sorts of conditioned reflexes have been formed in this animal, what stimuli from the internal organs and the external world are acting upon it at a given moment, what its response reactions to these influences will be (and accurately describe these reactions), and when they will occur? It is clear that all these questions must be answered in the negative. That is why the methods of investigation that were introduced by Pavlov, and to which we adhere, not only retain their importance today but will continue to be important in the future.

The physiology of higher nervous activity that Pavlov created has as its purposes the study of the mechanisms of nervous processes and the functional organization of the brain, the study of those brain functions that ensure the animal's (appropriate) interrelations with the surrounding world (the animal's behavior), and the utilization of physiological knowledge for the understanding of subjective phenomena: all these under both normal and pathological conditions.

The irradiation of nervous processes plays an important role in the activity of the brain. Excitation initiated by an external stimulus spreads extensively through the brain, selectively involving different regions of the brain to different degrees, and thereby promoting coordinated and unified functioning. As it pertains to the hemispheres, this property was studied by Pavlov under the name of "the law of irradiation and concentration of the processes of excitation and inhibition." We need not dwell on facts that are known to everyone, although they have been the object of sharp criticism from certain authors who have misinterpreted them.

Let me begin by setting forth some recent data of ours pertaining to the irradiation of excitation under the influence of unconditioned stimuli. General patterns established for lower nervous centers always are reflected in the function of the brain as a whole.

It was of interest to choose two secretory centers and show the effect they have on each other as a result of the irradiation of excitation. For this purpose we selected the salivary and lacrimal nervous centers. Dogs with externalized salivary and lacrimal ducts were used in the experiments; the operation on the lacrimal glands was developed by K. S. Abuladze.

If we feed a dog or irrigate its mouth with an acid solution, we observe that tears are secreted as well as saliva. The reverse is also true; stimulation of the

conjunctiva with a weak acid solution or mechanically with a wad of cotton results in secretion of saliva as well as of tears. This shows that the process of excitation evoked by the corresponding stimuli not only irradiates in the brain within the immediate centers of the given stimulus, but also involves other centers that do not bear a direct relation to these stimuli.

The fact that this is a matter of irradiation, that specific excitation from the primary nervous center reaches the second center, may be seen from the following.

When the conjunctiva is stimulated mechanically, lacrimation begins after two seconds, but salivation begins after 5 sec. If a meat-biscuit powder is eaten, salivary secretion is observed after 2 to 3 sec., but lacrimation is not seen until after 20 sec. When the oral cavity is irrigated with an acid solution, salivation begins after 2 to 4 sec., but lacrimation begins only after 40 sec. The conclusion is that when the oral cavity is stimulated a comparatively weak excitation reaches the lacrimation centers; more time is required before the weak impulses summate sufficiently to give a distinct secretory reaction.

Moreover, the chemical composition of the tears is different, depending on whether they are secreted in response to stimulation of the oral cavity with food or acid. The concentration of proteins in the tears secreted in response to eating food is several times greater than that in response to acid. That is, tears secreted in response to eating the meat-biscuit powder contain about 15 mg. of protein per milliliter, whereas tears secreted upon stimulation of the oral cavity with acid contain only 5.7 mg./ml. of protein (I. A. Lapina's experiments). We may conclude that a qualitatively different excitation process irradiates to the centers for the lacrimal glands in these two cases: a fact of considerable importance for our understanding of brain activity.

The irradiation of excitation is determined not only by the properties of the nervous process evoked in the primary center, but also by the functional state of the nervous centers to which the excitation spreads. If before the oral cavity is stimulated we first stimulate the conjunctiva, the secretion of tears increases approximately twofold. Therefore, after stimulation of the conjunctiva a state of elevated excitability or latent excitation remains for some time in the lacrimation center. Some of the nerve cells of this center, which were already subliminally excited, send forth a wave of propagated nerve impulses as a result of summation. This is one of the phenomena that Pavlov called the summation reflex.

There is reason to think, however, that this is not just a matter of simple summation, but that the excitation process irradiates preferentially to the focus whose excitability is increased, or to the center of stronger excitation. This rule is of great importance for the formation of conditioned reflex connections. The interrelationships that obtain may be schematically depicted as follows. Let us suppose that six single waves of excitation irradiate from center A to centers B and C. Of these units, four represent intense waves of excitation—two going to B and two to C—and two waves are weak, dying out along the way before reaching these centers. If we first create a state of elevated excitability in center B by stimulating it directly, the weak wave will now reach it, and B will receive three units of excitation, while C receives only two,

as before. If the excitation in center B is made stronger still, it is possible that a diversion will result, and that some of the waves of excitation that had previously gone to center C will now be directed to B.

Here are some of our results. When a dog is fed, the resulting parotid secretion is approximately equal on the two sides. Before the dog had eaten, however, one of the externalized areas of the tongue (for example, on the right side) was painted with an acid solution and we waited until salivation in response to this stimulation stopped completely and the nervous center returned to the resting state; after this we again gave food to the animal, and salivation from the right parotid was significantly increased.

We have not performed experiments of this type on decorticate dogs, and we still do not know how much of this summation reflex can be attributed to lower centers and how much to the hemispheres (that is, how much can be ascribed to the so-called cortical representation of these unconditioned reflexes). But the same pattern can be seen in motor reactions of an animal in which there is no doubt that the cortex participates.

We can often observe such behavior in the formation of motor conditioned reflexes in which a dog is supposed to go to one table in response to the first of the conditioned stimuli and to another table in response to the second. If food is given at table A after the conditioned stimulus is applied, and this is repeated several times in succession, the dog will subsequently go to table A even in response to the application of a second conditioned stimulus followed by the presentation of food at table B. This happens in the initial period of formation of conditioned reflexes, while they are not yet stabilized.

Concentration of the excitation process is also closely related to irradiation of the process. If no other conditions interfere, then upon repeated application of the unconditioned stimulus the extent of irradiation diminishes and the excitation process becomes more concentrated. For example, following acid stimulation of an externalized area of the tongue on the left side, salivation occurs chiefly from the left parotid gland, but there is also a small amount of secretion contralaterally, from the right gland. In response to repeated stimulation, the secretion from the right parotid gradually diminishes and then completely disappears. The excitation process becomes more concentrated and affects only the centers of the left parotid. Once created, this state of concentrated excitation remains for many hours.

Unconditioned reflexes are based on the innate functional organization of the nervous system. This innate functional organization is also the basis of the property of irradiation and concentration of nervous processes and the phenomenon of the summation reflex. In turn, these properties promote the formation of the new functional organizations of the brain that arise during the development of conditioned reflexes. As for the summation reflex, it undoubtedly constitutes the first step in the formation of a conditioned, temporary nervous connection.

The intimate mechanism of formation of a temporary connection is still unknown, and it is my impression that the latest investigations in the area of brain physiology have not brought about any radical change in this respect. However, we do have some important information as to the functional organization of nervous processes in conditioned reflex activity.

Some time ago we showed that the nervous processes in the brain may be divided into processes resulting in external reactions and processes that establish only the over-all tone of the brain, that is, processes of general activating significance, both positive and negative (leading to elevation or reduction of tone). We were unable to localize the processes of the second type, to ascribe their occurrence to any definite morphological structure in the brain, or to establish their fundamental mechanism. Now, however, since the brilliant work that has come primarily from the laboratory of Horace W. Magoun, disclosing the function of the reticular system, this whole problem has entered a new phase of development.

The essential fact we were able to establish at the very outset, which is our contribution to the physiology of the brain, consists in our discovery that these processes of a general activating character can be reproduced by conditioned reflex means: that they can be elicited by influences in the experimental situation that had no such effect prior to the formation of the temporary connection. It follows that we may speak of particular conditioned reflexes in which the reaction to the external stimulus culminates not in a definite external reaction but, on the whole, only in a change in the functional state of the brain, a change in the tone of certain divisions, or mechanisms, of the brain. We therefore called such conditioned reflexes "truncated" conditioned reflexes.

Reflexes of this type, both of a general and of a more local character, constantly take part in conditioned reflex activity. In the formation of a conditioned reflex, the excitation process evoked by a given conditioned stimulus first begins to irradiate preferentially to the centers of the unconditioned reflex and finally fuses with the process of unconditioned excitation in a single combined nervous process. This is primarily shown by the fact that the conditioned stimulus activates the centers of the unconditioned reflex and affects its execution, increasing its magnitude, speed, and accuracy. These data of ours have recently been substantiated in the work of J. P. Segundo of Montevideo, Uruguay (personal communication).

The particular conditioned stimulus that directly elicits the conditioned reaction is not the only stimulus connected with the unconditioned reflex; various extraneous stimuli and numerous components of the experimental situation are also connected with it. These factors increase the excitability of the unconditioned centers even before the conditioned stimuli are applied, preparing these centers for the subsequent action of the unconditioned stimulus and for the most effective unconditioned reaction. This also happens by the mechanism of truncated conditioned reflexes.

At present we still do not have accurate data concerning the question of the sequence of occurrence of the nervous processes in the various divisions of the brain in conditioned reflex activity, or how they are united in a single complex nervous process, or the final functional organization of this process. However, it is possible to isolate a few fundamental elements in this organization: the activity of the cortical portions of the analyzers (that is, cortical projection zones); the activity of the cortical representation of the unconditioned reflexes; the activity of the unconditioned centers; the activating mechanism of the reticular system, located in various subcortical divisions of the brain; and possibly also an analogous mechanism within the cortex itself. A special

position is occupied by the activity of the central nervous elements of the motor apparatus responsible for the execution of the so-called voluntary movements. In man, finally, all of this is crowned, according to Pavlov, by the function of the second signal system, which ensures the function of speech. All of this operates as a coordinated whole.

If conditioned reflex experiments are conducted day after day and the conditioned stimuli are applied in a definite constant sequence, there results that organized functional structure of temporally correlated nervous processes that Pavlov called the dynamic stereotype. I spoke of this in greater detail at the Moscow Colloquium on the Electroencephalography of Higher Nervous Activity in 1958.

When a coordinated system of conditioned reflexes is developed on this basis, the nervous processes that are generated during the application of the conditioned and unconditioned stimuli and those that occur in the intervals between the applications of the conditioned stimuli constitute a complex nervous process that is temporally integrated and proceeds in an orderly fashion. In this case, even before the recurrent application of the conditioned stimulus an elevation of the excitability of the centers of the conditioned stimulus occurs. This elevation of excitability may be so great that spontaneous reactions occur, motor as well as secretory. In the case of conditioned food reflexes the dog may persist in looking in the direction from which the conditioned stimulus ought to be heard. Obviously this is the phenomenon that psychologists call attention and expectancy. First there is a general alimentary excitation, a general preparation for future alimentary activity, the expectation of feeding in general that is supposed to follow. Then the reaction is concretized, and the animal awaits the definite conditioned stimulus that is followed by feeding, and focuses its attention on this stimulus.

Everything I have said so far is only a schematic representation, of course, but it can be regarded as correct since it has been confirmed by experiments of many sorts. For example, Jiurgea in our laboratory was able to form a conditioned reflex to stimulation of the visual cortex by implanted electrodes, combining this stimulation with stimulation of the motor cortex, also with implanted electrodes. He repeated these experiments in the United States, working with Doty. Here, the fundamental condition for the successful formation of a conditioned reflex is that a definite interval be allowed between successive combinations of conditioned and unconditioned stimuli: a definite, sufficiently long interval of time. If the time interval between two successive trials is too short, the first stimulation of the visual cortex (conditioned stimulation) will be connected with the second stimulation of the motor cortex (unconditioned stimulation) to the same extent as the second with the first, and the necessary directedness in the total nervous process will not develop. For this reason it is impossible to obtain a distinct conditioned reflex under such conditions. This fact itself, therefore, is an illustration of the formation of a complex, long-lasting nervous process during the development of a conditioned reflex.

By making use of the fact that during the formation of a conditioned reflex the excitability of the centers of the conditioned stimuli increases until a

spontaneous reaction occurs, we have been able to obtain an active reproduction of involuntary reactions as conditioned "excitators" of the alimentary reflex: specifically, to obtain a conditioned shaking-off reflex. If the dog is given food every time it shakes itself during the experiment as a result of whatever skin stimulations may have arisen, it begins to shake itself more and more frequently in this experimental situation. The general alimentary excitation, irradiating to the centers of the shaking-off reflex, will elevate their excitability; and weak skin stimulations (irritations) that are always present and do not normally elicit the shaking-off reflex become supraliminal and adequate to elicit the reflex. Eventually the dog begins to shake itself actively, so effortlessly, so accurately, and so often that this essentially involuntary act cannot be distinguished from voluntary movements.

We believe that voluntary movements arise by the same mechanism when they become the first components of motor alimentary conditioned reflexes.

Currently, we are studying the completely normal behavior of animals when their freedom of movement in a large experimental room is not restricted, with the experimenter being isolated from the dog. This behavior can be satisfactorily explained, without artificiality, on the basis of our concepts of the properties and organization of the nervous processes of the brain.

In conclusion, I propose to discuss certain data on the irradiation of nervous processes in pathological conditions.

In various difficult nervous problems—particularly often during overstrain of internal inhibition in cases of delayed conditioned reflexes—we have repeatedly obtained extreme, abnormal irradiation of inhibition. The first deviation from normal is a marked reduction in the magnitude of the secretory conditioned reflex; in the next stage the secretory response is absent throughout the entire application of the conditioned stimulus. Inhibition, normally present only in the first phase of a delayed reflex, remains throughout the entire second phase of the reflex. Later, secretion begins to disappear even in response to the unconditioned stimulus. The dog may eat for 20 seconds without secreting a drop of saliva. If this pathological state is intensified, the dog does not take the food presented to it immediately, but hesitates for a few seconds, that is, the inhibition now spreads to the motor centers as well. Finally, the inhibitory process irradiates to such an extent that the dog absolutely refuses to eat.

We have called this phenomenon pathological irradiation of the inhibitory process, since the inhibitory process spreads abnormally and very extensively. The whole phenomenon is undoubtedly initiated by the cerebral cortex, since delayed conditioned reflexes cannot be obtained in the decorticate animal. However we ought not to represent the inhibitory process, as such, as spreading from any individual cortical point, involving other divisions of the cortex and the subcortex. The inhibitory influences spread from the cortex, but such influences may have several starting points.

We ought to add that in the animal's subsequent behavior not everything will depend on pathological irradiation of inhibition. All pathology of higher nervous activity is permeated by the mechanism of formation of pathological conditioned connections. Various pathological functional states and reactions

are stabilized and reproduced under particular external influences. They may be very persistent and hard to remove. In some instances such pathological connections remain for years. We have a striking example of this in the case of attempts to form a defense motor conditioned reflex to acid stimulation of an exposed area of the tongue (I. A. Lapina).

Another example of pathological irradiation of nervous processes can be illustrated by the following experiments. A dog is taught to lie quietly in its stand with small electric lights fastened close to its eyes. At 5-min. intervals these lights are permitted to flash for periods of 20 sec. One eye is stimulated by light flashes at a frequency of three per second, and the other at a frequency of seven per second. From M. N. Livanov's data we know that it is difficult for an animal to tolerate stimulation of the eye with light flashes in a rhythm that differs from the normal discharge rhythm of cortical cells. W. Grey Walter has shown that, in man, stimulation by flickering lights is accompanied by unpleasant sensations and, in persons with a tendency to epilepsy, it may provoke epileptic seizures. According to I. V. Danilov's experiments, stimulation of the eyes by asynchronous light flashes is an even greater challenge to the animal's nervous system. Asymmetry of cortical potentials in the two hemispheres develops. Then wave-spike discharges appear, which are characteristic for epilepsy, as Jasper has shown. Furthermore, when such experiments are carried on day in and day out over a long period of time, the dogs develop clonic and tonic contractions of the hind-limb muscles. Such hyperkinesias become very stubborn; they arise not only upon stimulation with light, but spontaneously as well, and they should be considered pathological.

Thus a nervous process of abnormal organization, generated in the visual cortex, irradiates to the motor cortex and produces a picture of hyperkinesia with the presence of nerve cell discharges of an epileptiform character.

I have been describing to you certain properties of nervous processes, established through the use of the fundamental method developed by Pavlov. I have tried to show how a knowledge of these properties makes it possible to study the complex organization of nervous processes that occurs in conditioned reflex activity, and to explain various facts about animal behavior. In our work we have followed our own path, which differs from the direction of the investigations that are being carried on in the United States. It is my hope that the exchange of views will increase mutual understanding and will promote further productive development of our knowledge of the activity of the brain.

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PAIRED SENSORY MODALITY STIMULATION STUDIED BY COMPUTER ANALYSIS

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It is a pleasure and an honor to follow P. S. Kupalov in these pages. Although not aware in advance of what his particular subject would be here, I know well his interest in the problem I should like to discuss briefly, namely, the neurophysiological basis of temporary connections.

The experiments which I shall report very briefly here are related to some proposals that have been made in relation to temporary connections, namely that convergence, onto the same neurones, of impulses from the different sense modalities may play a part in closure of these connections. Experiments that I have made have been directed toward a questioning of the word "temporary" and to questioning whether a site of convergence necessarily means a site of closure.

It is well known that among the subcortical structures, responses to all sensory modalities can be recorded in certain regions of the reticular formation[2, 18,28] and these electrophysiological data have been used as the basis for Fessard and Gastaut's,[17] for Gastaut's,[20,21] and for Buser and Roger's[12] proposals that the brain stem may be a major initial site of closure. This suggestion contrasts with the view widely held by the pupils of Pavlov that the cortex plays the primary role,[5,25,29,33] with subcortical structures subserving as only primitive "temporary connections."[26]

The cortex and midline structures of the brain stem are not the only candidates for a site of convergence of impulses from many sources. In that other great system of the brain, the limbic system, for example, the amygdaloid nuclei[27] and hippocampus are meeting grounds for afferent signals, however indirectly conveyed, and are known to distribute impulses widely to other structures.[1,16,19,24]

It would seem to us that the mere demonstration of a site of convergence does not in itself yield evidence of a useful functional connection. A gross alteration of behavior in an animal would demand some brain mechanism that evinces a major change as the result of temporal contiguity in these sites of convergence. The message sent to the rest of the brain from these sites, when paired sensory modalities impinge on them, must surely be coded differently from the messages they send out in the absence of this temporal contiguity. Such a message reasonably could be expected to reveal its arrival in other centers, both cortical and subcortical.

It is proposed that the greatly changed firing pattern consequent to pairing of sensory modalities, an effect presumably carrying information, would result in a change in distribution of activity within the brain that may be detectable, on a statistical basis, by sampling with gross electrodes. Should this concept have any basis in fact, responses evoked by stimulation of more than one sensory input should be detectable, after pairing of stimuli, in centers that

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receive projections, direct or indirect, from the structures that contain these neurones of convergence.

Our laboratory work designed to test some of the suggestions made above is still in progress, but a few examples of our results can be shown. The studies to be reported here were not on conditioning in any behavioral sense, but are solely electrophysiological observations of response systems in the brain.

In choosing the stimuli to use for this work it has seemed to us that the above hypothesis is better tested by physiological stimulation by the actual sense modalities than by electrical shock to the afferent nerves, since the latter results in a highly synchronized volley and an artificially intense temporal contiguity at the sharing neurones. We have, therefore, used flash and click and not nerve stimulation. This short report will also be restricted to the experiments in which the stimuli were given synchronously and not serially (as in conditioning experiments).

In the experiments to be reported, all the animals were unanesthetized freely moving cats in whom cortical and depth electrodes had been implanted stereotactically under full surgical anesthesia approximately one month before the first recordings were taken. Since in the unanesthetized animal some of these responses may be hidden by the on-going electrical activity of the brain, we have used various forms of automatic averaging computers that effectively emphasize those potential changes that are time-locked to the incidence of the stimulus and average out the potentials that are only randomly related. These computers have been described by their designers,[3,4,14,30] and results obtained with them have been reported in previous publications from this laboratory[6-9] and from our colleagues in the laboratory of Communications Biophysics and the Lincoln Laboratories of the Massachusetts Institute of Technology, Cambridge, Mass.[22,23,30-32] These devices, in brief, increase the signal-to-noise ratio.

FIGURE 1 is introduced to illustrate the type of recordings we obtain from the Average Response Computer (ARC), and shows the average wave form of the response to flash recorded simultaneously in the reticular formation, the centre median, the nucleus centralis lateralis, the caudate, and the visual cortex.

In FIGURE 2 some responses to click are shown. Responses in the auditory cortex are so much greater than those in other regions that their average is shown at half the amplification used for the next largest response (in the inferior colliculus), at a quarter the amplification for the reticular formation, and at an eighth the amplification used for the centre median. I shall not present recordings of all the sites in which we find responses, but I might add that when we compare responses in the anterior hippocampus we find both click and flash represented, the latencies varying with the position in the hippocampus in which the electrode lies.

Results of Pairing Flash and Click

Taking only three of the sites that respond to both flash and click, the following represent a mesencephalic, a diencephalic, and a limbic locus respectively.

Reticular formation. The response to the flash used was always larger than that to click but, when paired, a further increase occurred; this was essentially in the first negative complex (that is, negative at the exploring electrode when unipolar recordings were made). This is shown in FIGURE 3, in which the amplification used for the recordings of click responses was twice that used for flash.

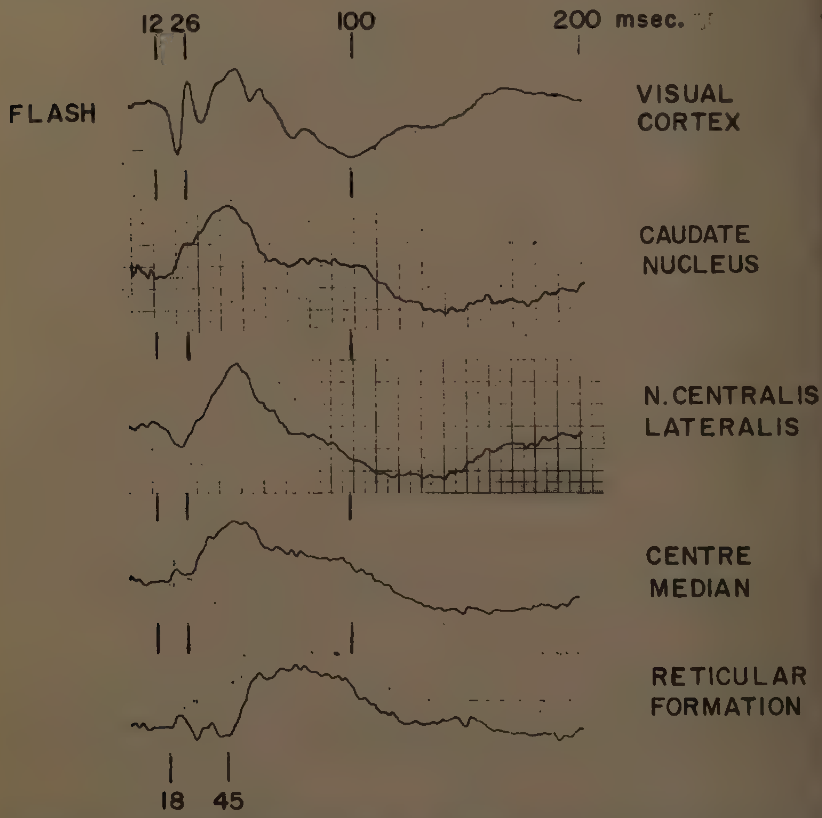

FIGURE 1. Responses to flash in various sites within the brain. The amplification used was the same for all records, with the exception of the visual cortex, in which the response was so large that only half gain was necessary. The numbers above and below the vertical lines indicate time intervals after the flash in msec. The ARC-1 computer was used.

Centre median. The response of the centre median to flash alone was larger than to click alone for the respective stimulus strengths used. When paired we found the response smaller in amplitude than with either stimulus alone as though there had been some inhibitory interaction (FIGURE 4). The wave form became distinctly bimodal, reflecting, no doubt, the two major grouped inputs: an early one from the click and a later one from the flash, and this temporal sequence makes simple occlusion seem unlikely. In other cats we have found this bimodal distribution even more marked, but with less evidence for reduction of total area under the curve.

Hippocampus. On pairing, the wave form of the response in the anterior hippocampus changed markedly, and it is noticeable that this new wave form, after 1200 pairings, was found to persist in the response to flash even after

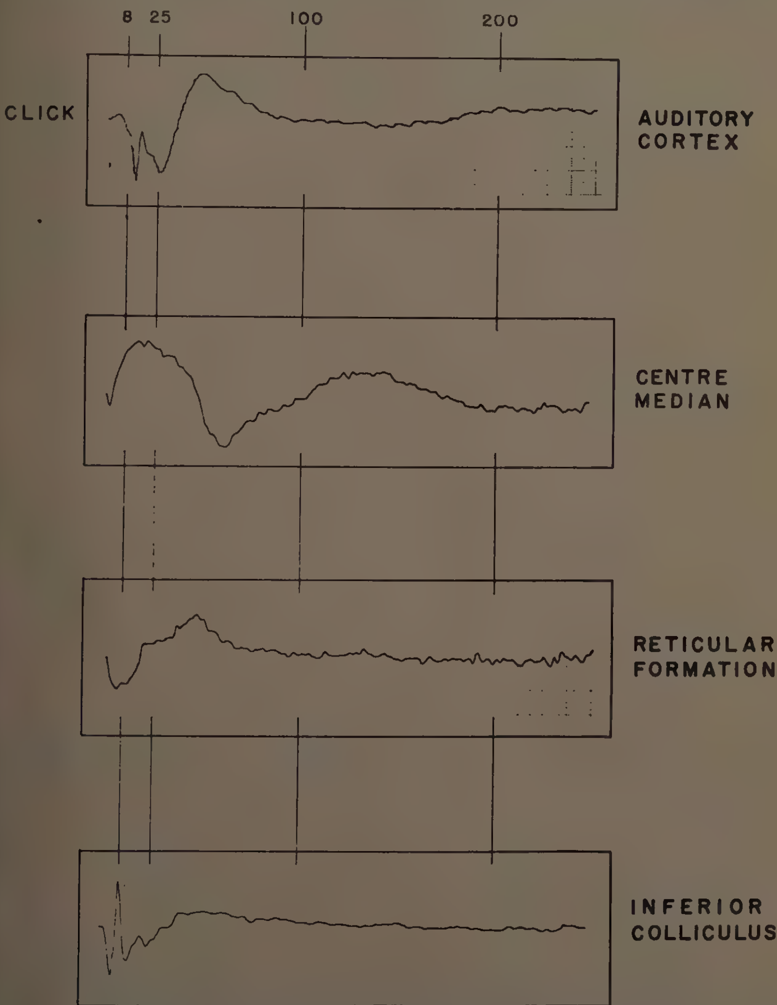

FIGURE 2. Responses to click in various sites within the brain. The relative amplifications used were as follows. Centre median: eight times that for auditory cortex; reticular formation: four times that for auditory cortex; inferior colliculus: twice that used for auditory cortex. The small numbers at the top of the chart indicate milliseconds after the click was administered.

the click stimulus had been dropped out. One is tempted to relate this persistence in the hippocampus to some of the currently clinical ideas related to memory mechanisms. As in the case of the centre median, there was a decrease in total activity during pairing as recorded by these electrodes (FIGURE 5).

Turning now to the cortex, it may be asked whether this synchronous pairing has any effect on the specific cortical response. FIGURE 6 shows recordings at the auditory cortex of the response to click alone, and to click paired with flash.

This figure shows no change in the initial surface-positive components but an almost twofold increase in the later surface negativity that is usually assigned to activity in superficial dendrites in the layers where the so-called nonspecific afferents are thought to play upon them.

A more subtle effect can be demonstrated if more pairings are made and averages over aliquot periods are computed. This is shown in FIGURE 7, in which a longer time scale is used in order to study late events (that is, those with latencies longer than 100 msec.). The first 390 clicks produced a larger surface negativity than the next 390, by a factor of 4 to 3, and the surface

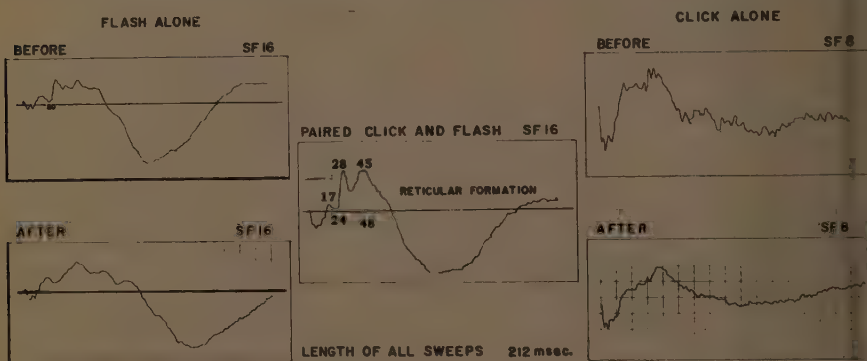

FIGURE 3. Responses recorded from the reticular formation to flash alone and to click alone (*left* and *right* records, respectively), before and after pairing these stimuli (*center* record). The numbers following the letters SF above each record indicate the setting of the gain on the computer, and are inversely proportional to the amplification used; that is, since clicks produce a smaller response than flashes, twice the amplification was used for the records in the right-hand column.

positivity that follows this at about 90 msec. after the click is also reduced on repetition of the stimulus.

This is, no doubt, the phenomenon of habituation. With the added stimulus of a flash paired with the click, the increase in response of the auditory cortex is again seen in all components except the primary positive deflection. But on persisting with the paired stimulus and taking averages of consecutive periods with an equal number of stimuli, this response to pairing is also seen to habituate; the surface negativity of both the first and second phases is affected, as well as the intermediate positive wave whose crest comes about 110 msec. after the click.

These experiments alone cannot define whether the great increase in size of the first sampling of responses to paired stimuli should be regarded as evidence that convergence, somewhere in the brain, has projected its influence by causing a greater influx to the primary receiving cortex, or whether this is an alerting effect produced by the introduction of a new stimulus.

Intensive studies of the orienting reflex have been made by Sokolov,[34] who has emphasized how this reflex is initiated by a change of stimulus—by any increase, decrease, or qualitative change, independent of the modality of the

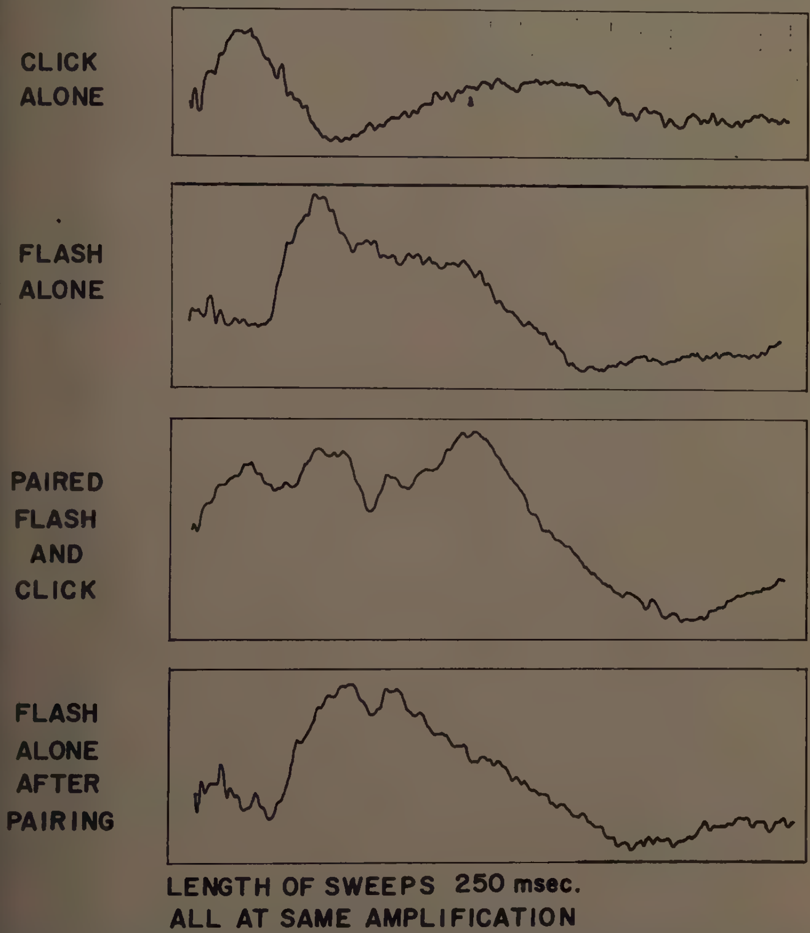

FIGURE 4. Responses recorded from the centre median to flash alone and to click alone followed by pairing of these stimuli and the repetition of flash alone after pairing. Amplification was the same in all records with the exception of the response to flash alone before pairing (*second from top*), which was very large and therefore was recorded at half the gain used for the others.

stimulating agent—and he has presented evidence for an excitatory process being set up by this change.

This would be one framework in which to view the increase in response when the stimulus is changed in our experiments from the single modality to the "novelty" of the paired modalities. In this case it is strange that we do not again find an increase of response when the stimulus again suffers a change, this time from paired to single modality.

Other experiments that, perhaps, may be considered in this context ar those of Chang,[13] who showed a facilitation in the auditory system where steady illumination was applied to the retina. Steady retinal illumination was found by Chang to increase the auditory cortex response to electric shock delivered to the medial geniculate, even after extirpation of the visual cortex

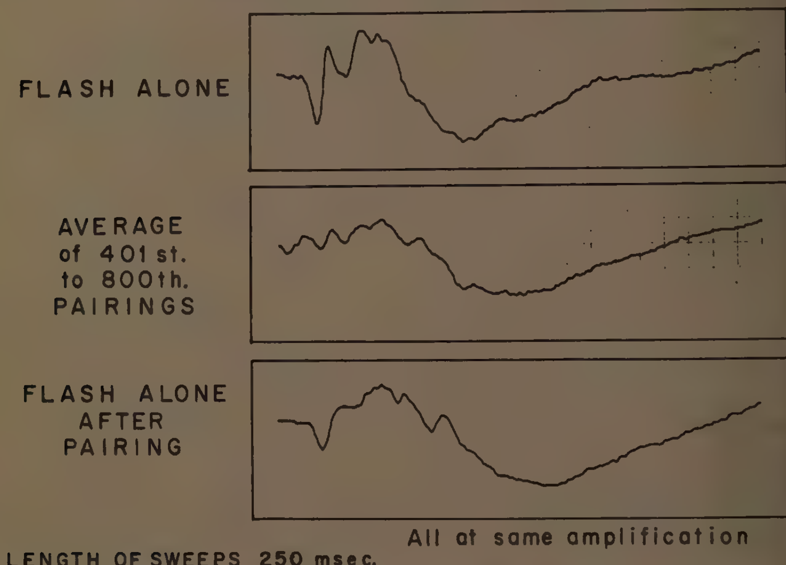

FIGURE 5. Responses to flash recorded in the hippocampus before, during, and afte pairing with click. Amplification is the same in all the records.

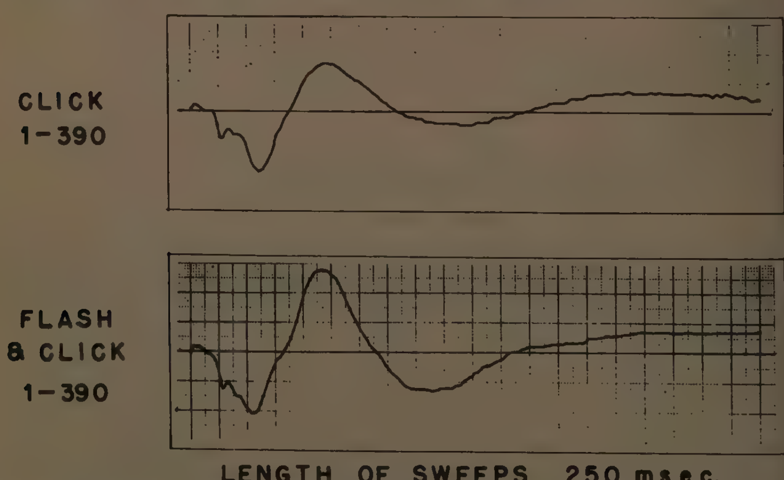

FIGURE 6. Effect of pairing a flash with a click on the responses of the auditory cortex Note the increase (by a factor of almost 2) in the surface-negative component of the respons when a flash is paired with a click. Amplification is the same for both records. In eac instance 390 responses were averaged.

In some experiments with more physiological stimuli, Sokolov[34] has demonstrated a facilitation by sound of the electroretinogram response to light. He believes that this influence takes place through participation of the reticular formation.

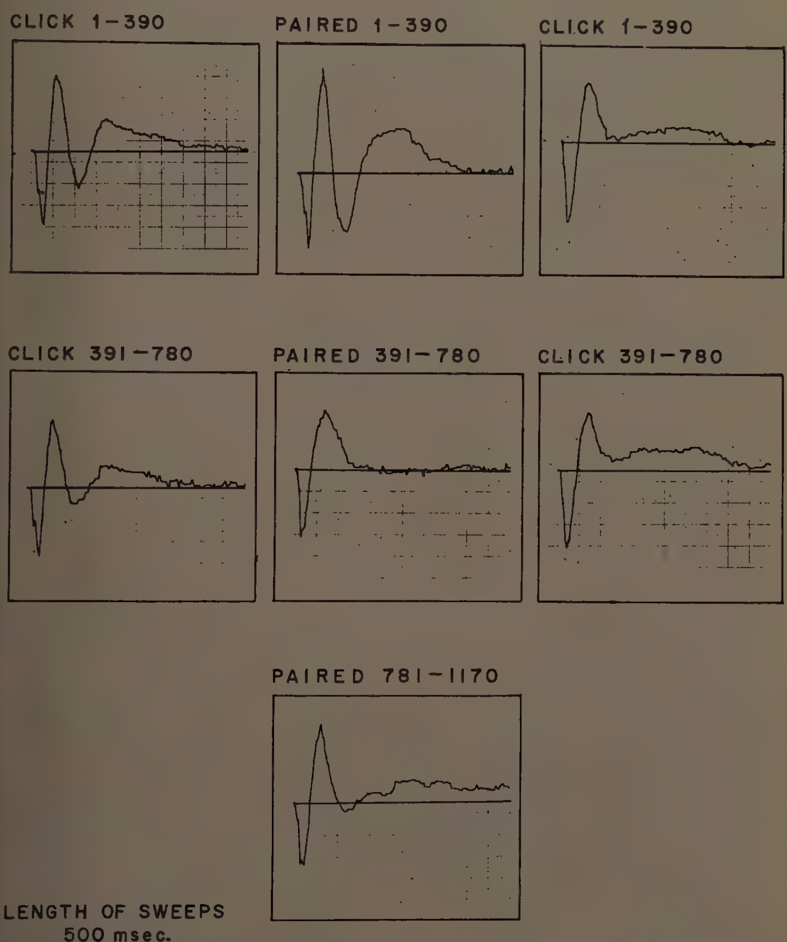

FIGURE 7. Auditory cortex response to click, the effect of pairing with a flash stimulus, and the appearance of habituation. Habitutation to click alone can be demonstrated by comparing the averages of the first 390 responses with the second 390. A marked increase in the surface-negative components occurs on pairing, and these are also seen to habituate on repetition (see text). Amplification was the same for all the records.

In considering whether the paired stimuli created a greater cortical response through their increased stimulating action on the reticular formation, thus producing a facilitation, one is reminded of the facilitation of the cortical response to geniculate stimulation found by Bremer and Stoupel[10,11] and by Dumont and Dell[15] on electrical stimulation of the reticular formation. Ac-

cording to Bremer, however, this facilitation could be produced only in a response evoked by a synchronized volley initiated at the thalamic relay or optic tract, and was not evident when physiological stimulation of the sense organ was employed.

Conclusions at this stage of our researches are necessarily restricted. Apart from other considerations, we have found that fluctuations in the state of alertness of the animal affect the results profoundly, as does also the exact position of the recording electrode. The latter observation is especially true for the hippocampus which, electrophysiologically speaking (as well as otherwise), cannot be regarded as a uniform entity.

In summarizing these observations, we may say that when the response can be selected from the background activity, it appears that there is a certain ubiquity of response throughout the brain, and that mechanisms for connection may not be temporary in nature, but are lying in wait. On pairing sense modalities we find, with our averaging techniques, changes in response in the reticular formation of the brain stem, in nonspecific nuclei of the thalamus in the hippocampus, and in the specific sensory cortex. As has been discussed in some sites the interaction appears to have an inhibitory effect, in others a facilitatory effect. In some regions of the hippocampus the interaction pattern may persist after pairing in a manner suggestive of storage. All effects however, may be regarded as reflecting the ensemble of a change in the coding of the information being distributed throughout the brain, a more global effect than is suggested by the concept of a single site of closure.

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DISCUSSION: PART IV

RICHARD L. SOLOMON (*University of Pennsylvania, Philadelphia, Pa.*): First, I express my appreciation to Kupalov for pointing out something that may have been in the back of my mind but had not sunk in: the repeated presentation of a conditioned stimulus may often sensitize or arouse a whole responding system so that an unconditioned stimulus may actually have a greater effect than it did before presentation of conditioned stimuli. This, evidently, is an important fact of the Pavlovian conditioning procedure.

Those of us who, like myself, do not often work with the Pavlovian conditioning procedure do not often come across such facts. However, I should like to point out that in the realm of instrumental avoidance training, which may obey slightly different laws than does Pavlovian conditioning, there are some very similar observations one can make.

An extinction procedure may be established if one trains a dog to avoid electric shock by responding to a given stimulus, and if one uses a contrasting stimulus in order to create a discrimination. The animal is taught to avoid one stimulus and to do nothing in response to the others. When the discrimination is perfected, the animal will consistently avoid the presentation of the first stimulus and he will consistently sit still or do nothing when presented with the other stimulus. In the extinction procedure there is a choice of many methods. For example, one may continuously present the neutral stimulus which has never been paired with shock, and then impose upon it, at intervals, the conditioned stimulus that has been paired with shock in the past and has proved indispensable in establishing the avoidance response. Alternatively, one may continuously present the stimulus that was paired with shock (which is the danger signal) then introduce periodically the neutral stimulus; this will show how the avoidance response behaves with respect to it and thus reveal whether the discriminatory differentiation is maintained.

The first thing one might think of is fatigue. In instrumental training we often consider the fatiguing of response systems, and one might think offhand that the constant presentation of the danger signal, the signal that was once paired with shock before the avoidance response was totally learned, might fatigue the avoidance response and thus produce more rapid extinction. Actually, in my experience, the reverse has been true, concurring very nicely with Kupalov's observation. If one presents the neutral stimulus over and over again during the extinction series, the one that the animal typically does not respond to, and then one tests intermittently with the positive stimulus, much more rapid extinction of the avoidance response is obtained than if one exercises the positive stimulus over and over again and tests periodically with the neutral stimulus.

Evidently the constant exercise of the response system paired with the conditioned stimulus makes the whole system more excitable. This is attested by the fact that presentations of the previously neutral stimulus—that has never been paired with shock—will often elicit avoidance responses during the extinction procedure when the positive stimulus is presented repeatedly or is presented more often than is the neutral stimulus.

I do not know how easy it is to convey, across two different experimental traditions, the similarity of concepts and how they are applied. In the Pavlovian conditioning laboratory, phenomena very often are looked at very differently than they are in the American tradition, which is typically Thorndikian and involves, whether we like it or not, concepts such as motivation, drive, and reward. I think the findings in each area can be used to cross-fertilize research in the other area. Findings in Thorndikian experiments are often very useful in application to Pavlovian conditioning and vice versa.

I propose to describe an experiment that makes an attempt to differentiate the Pavlovian conditioning procedure from the typical American instrumental training procedure (which our Soviet colleagues are apt to call a motor conditioned reflex). The one big technical barrier to studying separately the development of learned instrumental responses and conditioned reflexes has been that they both usually take place simultaneously in most training situations. If a freely moving dog is trained to press a panel in order to get food whenever a signal light is presented, the dog readily learns to press the panel to get the food if he is hungry; he will also develop a conditioned salivary reflex during this training process.

In analyzing the results of such experiments it is very difficult to know whether the two learning processes go on independently and simultaneously, whether one is necessary for the other, or vice versa. One might argue that the animal has to develop a conditioned salivary response before it can really learn to press the panel effectively, or one may argue that the procedures are independent and follow separate laws.

My colleagues and I performed an experiment in which we separated the two procedures with the help of the pharmacologist and his new curarelike agents. One can present an animal with a conditioning procedure as carried out in the Pavlovian laboratory and, with the help of curare drugs, totally immobilize the animal skeletally so that he can make no instrumental responses or motor reflexes. This technique enabled us to study the two procedures described above and see how they interact.

A group of dogs was trained to avoid shock when a danger signal was presented by means of pressing a panel. A Pavlovian delayed-training procedure was used. The signal stayed on for 10 seconds, following which the shock was administered. If the animal pressed the panel we could remove the shock and the signal simultaneously. The development of the avoidance responses was characterized by short-latency panel presses in response to the danger signal.

When the animal achieved a criterion of 20 stable avoidance responses, 3 seconds in latency or less, he was then totally curarized. He had learned to press a panel in order to avoid shock, and now he was totally curarized using an overwhelming dose of *d*-tubocurarine: that is, he could not respond to anything that was presented to him; at least he could not respond skeletally.

Then the animal was given Pavlovian conditioning procedures while under curare, during which two new stimuli were introduced to the situation. The original stimulus had been a dark flash, a light going out. Now we switched to the auditory modality and presented one tone of one frequency, always

paired with shock to the hind feet, and another tone of another frequenc that was never paired with shock. These tones were presented in randon order, and 99 such training trials were run, ending with the positive tone, th one that was paired with shock.

Presumably this was the typical presentation procedure for developing differentiated conditioned reflex. We had evidence that this happened, be cause many of the animals developed a cardiac acceleratory conditioned refle to the conditioned stimulus, the tone that was paired with shock, and the showed differentiation, that is, little or no cardiac response or less of a cardia response to the neutral stimulus that had never been paired with shock.

Thus we had an animal that was conditioned in a defensive reaction, cardiac reaction, but is totally curarized so he can do nothing about what h has been trained to know; in the past he had received avoidance training wit a conditioned stimulus different from the two auditory stimuli used in th later tests.

The animal was allowed two days to recover from the side effects of the cura rization and he was brought back into the panel-pressing situation. We the tested him on all three stimuli: the original conditioned stimulus to which h learned to avoid shock and the two discriminative conditioned stimuli whic he could not have learned to avoid but to which he did acquire cardiac cond tioned reflexes.

We have good evidence that the training or the conditioning under cura is transferrable to the instrumental state, even though no instrumental re sponses were ever paired up with the two discriminative stimuli while th animal was curarized. The animals typically press the panel when they hea the tone that had been paired with shock, and they typically refrain from pressing the panel but show more of an investigatory reflex when the stimulu that had not been paired with shock under curare is presented. Here we hav a case of transfer of training from an original *instrumental training* situatio through *conditioning* carried out under curare.

We are now proceeding to investigate the interrelationships between th parameters of these two types of training situations. For example, we desire t know what variables determine the degree of success in transferring the con ditioning experience under curare to the normal responding state when th animal can press the panel. These parameters are unknown. For anothe example, the time interval between signal and shock may have to be quit similar across the two situations in order to get this transfer phenomeno However I think the important point to be emphasized in this monograph that it is possible, using modern pharmacological techniques, to separate th Pavlovian conditioning procedure from the instrumental training procedu and study the interaction between the two when they are brought togeth in testing situations.

In conclusion, I should say that this procedure probably could be used f appetitive or alimentary conditioned reflexes as well as for defensive one One need not necessarily have training situations and conditioning situatio in which instrumental learning and Pavlovian classic conditioning are confuse These can be separated by the artificial procedure I have described.

Robert G. Heath (*Department of Psychiatry and Neurology, Tulane University School of Medicine, New Orleans, La.*): Several aspects of Snezhnevsky's paper were of particular interest to me; some because of my activities as a teacher of psychiatry; others because of overlapping research interests.

Snezhnevsky's use of Magnan's chronology in paranoia is a most useful take-off point for investigating the relationship between learning experience and the paranoid development. Four principal stages are considered by Magnan: first, the hypochondriacal stage; second, the referential; third, the persecutory; and the fourth, grandiosity. Occasionally a fifth stage is considered: that of deterioration. Many patients clearly exhibit symptoms of all stages in the order listed by Magnan. In some cases, however, the stages appear to be telescoped and some stages, seemingly, may be missed completely. The fact, however, that these are the stages through which the paranoid progresses serves a useful purpose in the investigation of the environmental experiences that contribute to this behavioral syndrome. In many clinics in the United States efforts are under way to relate symptoms to the early learning experiences of the individual. As a result of such studies of the paranoid, it has been possible, on the basis of the symptoms presented, to predict with some degree of accuracy the nature of the background learning experiences of the patient. Such experiments put psychodynamics on a more sound basis.

In the paranoid development we quite consistently find that the early faulty learning has been in the area of sexual behavior. To use the Pavlovian terminology, there has been faulty conditioning. The patient has been conditioned to fear the sexual act; thus, rather than being a pleasurable experience, it is shrouded in an attitude of fear and anxious expectation of punishment and injury. As a consequence, when the paranoid patient is in a state of sexual arousal he begins to think in terms of bodily injury. This, then, becomes the basis of the hypochondriacal symptomatology. When the conditioning, for example, is illustrated by the commonly voiced threat, "If you do that bad thing, no one will have anything to do with you" and, if it is stated that the results of this activity will be observable, then referential symptomatology is in the foreground. It is not my intention here to give a complete presentation of the paranoid syndrome. I wish only to point out that the other symptoms in the Magnan development similarly are complications in the faulty conditioning in the area of sexual behavior.

Most of the data concerning the nature of the paranoid development, that is, the specific influences of the learning experiences in creating this pathological syndrome, have been gathered in working with the more intact paranoid patients: those more appropriately labeled as paranoid characters or paranoid neurotics. These patients are in contrast to the group diagnosed as paranoid schizophrenics. The development of the syndrome in the paranoid schizophrenic group is more complicated since, in addition to the influence of the faulty learning experiences, an underlying disease process that alters brain function, schizophrenia, is present. The picture we see in this group is a combination of the effects of the learning process in which the psychodynamic conflict is essentially as in the neurotic, and a more severe, disintegrated type of behavior in which the symptoms are more in the open because of the associated,

underlying brain disturbance. As Snezhnevsky indicates, the learning process alone cannot completely and adequately explain the symptomatology of the paranoid schizophrenic.

In studies at Tulane, my colleagues and I assume that there is a more basic disturbance that affects the brain and thereby lights up, or brings into the open, the symptoms we associate with the disease process. Analogous situations exist in regard to other disease processes that affect the brain. Patients with congenital syphilis and symptoms of general paresis often display overt symptoms similar to those seen in paranoid schizophrenics after this disease process has affected the brain. Similarly, in association with certain toxic and nutritional states, latent personality factors will come forth and the patient will exhibit overt psychotic symptomatology. The complete nature of the factors affecting the brain in schizophrenic patients is not known as it is in the other states given as examples. We at Tulane, however, are of the opinion that the psychosis-inducing fraction we have isolated from the serum of schizophrenic patients, which induces overt symptoms of schizophrenia in nonpsychotic volunteer subjects, is a definite step toward establishing the nature of this disease. It ultimately may prove to be the factor responsible for the disruption of brain activity in the psychotic, schizophrenic patient.

Our experiments with the administration of taraxein (the name we have given to the psychosis-inducing fraction) to nonpsychotic volunteer subjects are proving to be interesting, and they support Snezhnevsky's concepts concerning the nature of the schizophrenic process. In one study, taraxein was administered to the same subject on two different occasions; his response with the second injection was different than the first. We conducted similar studies on other volunteers. On one occasion, a subject became catatonic, whereas on a subsequent administration of taraxein he developed symptoms resembling paranoid schizophrenia. The psychological make-up of the subject obviously was the same on both occasions. Therefore the symptomatology could not be explained purely on the basis of psychological factors. In another study, we pooled several doses of taraxein for administration to a number of volunteer subjects. A variety of symptoms appeared in the subjects although they had received the same substance administered at the same dose level. For example, one subject developed symptoms characteristic of the catatonic schizophrenic; another, symptoms characteristic of the chronic undifferentiated schizophrenia; a third, symptoms of the paranoid schizophrenic. Here, again, we could not render a logical explanation of all aspects of the pictures that developed. In still another study, four analytically trained psychiatrists interviewing the subjects who were to participate predicted, on the basis of their psychodynamic observations of each subject, the subcategory of schizophrenic symptoms that each would develop. The predictions were based on the prevailing concept that psychological factors in the prepsychotic personality are determinants in the ultimate symptomatic picture the patient will display. Among the psychiatrists, there was universal agreement concerning the clinical picture that each volunteer was predicted to develop. With the administration of taraxein, however, the subjects did not develop the predicted symptoms. This study also supports Snezhnevsky's observation that psychological factors are not the sole determinant of the ultimate clinical picture that schizophrenic patients develop.

The next point in Snezhnevsky's paper that I wish to discuss concerns the toposcopic recordings he presented. These were quite impressive. On the basis of our experience at Tulane over the past 12 years with cortical and subcortical recordings obtained from a series of 40 schizophrenic patients and 8 nonpsychotic control patients, his data make a great deal of sense. As I demonstrated during my discussion of Kupalov's paper, we at Tulane consistently have noted marked changes in recordings from specific parts—septal region, hippocampus, and amygdala—of the olfactory brain in association with psychotic behavior. When we have recorded from the bare cortex in addition to the subcortical structures and the scalp, we were not able to correlate changes in the cortical recordings with alterations in behavior. We were able to make this correlation only with the deep recordings, and it was striking and consistent. Before we initiated human work we anticipated, on the basis of animal experimentation, that we should detect changes on cortical recordings in association with fluctuating behavioral states and the altered recordings from the septal region. This assumption was based on animal experiments, in which Robert Hodes was the principal investigator, that demonstrated that septal stimulation produced diffused facilitation of the brain and, more specifically, that facilitation induced cortical background motor activity. On the basis of our animal experiments and our later human experiments, we have been led to consider the psychotic process in a framework very similar to that of Pavlov. We postulate that basic activating circuits involving the septal region, hippocampus, and amygdala are disrupted or functionally interfered with possibly by an underlying metabolic disorder. Our recordings demonstrate that this is indeed the situation: these subcortical structures are functioning abnormally. We assumed that, as a consequence, over-all cortical activity probably was retarded. However, we have not been able to demonstrate this latter phenomenon, that is, the actual slowing of cortical recordings, with our techniques.

It was interesting to note that Snezhnevsky had made consistent correlations between recordings and specific symptomatic constellations or clinical subcategories of schizophrenia. In our studies at Tulane, we were able to demonstrate some differences between the overactive, deluded paranoid group, and the underactive, retarded, hallucinatory, catatonic, hebephrenic group. There was a difference in frequency: in the overactive group, the rate was faster and the spikes sharper in the septal recordings; in the catatonic, hebephrenic, or retarded group there was more slow activity in the recordings from the septal region.

The toposcopic data of cortical recordings are very exciting, and they tend to prove what we had suggested and postulated in our theoretical conceptualization of schizophrenia:[1] namely, that as a result of impaired function of the deep regions of the brain, there is an alteration in over-all cortical function.

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GREGORY RAZRAN (*Department of Psychology, Queens College, Flushing, N. Y.*): I shall take the liberty of raising the general question of the relation

of irradiation to generalization. Both in the Soviet Union and in the Unite States generalization admittedly denotes the behavioral phenomenon that an organism conditioned to stimulus a_1 will also manifest some conditioning to a_2, and irradiation stands for an assumed or observed underlying neural mech- anism. However it appears to me that there are a vast number of cases o generalization in which mechanisms other than neural irradiation are indicated I have in mind five such types of cases. In the first type, generalization occur merely because there is no capacity for differentiation. The organism i incapable of differentiating between stimuli a_1 and a_2 and *ipso facto* generalize from one to the other. Fish generalize their conditionings more than do tur tles, but this is nothing for which the fish need be proud. This type of gener alization is really a pseudotype, an experimental artifact that would not re quire discussion except for the fact that such a large portion of reported result fall within it. Lashley[1] called it "failure of association," Woodworth an Schlosberg[2] termed it "nondifferentiation," and I[3] suggested the term "pseudo generalization."

I can illustrate the second type, I think, with some data from my own experiments. If I condition a human subject to secrete saliva to the beating o a metronome while the metronome is in sight of the subject, the very sight o the metronome, without beating, later will produce a certain amount of con ditioned generalization. We have here what might be called "residual generalization, which is really nothing but a common phenomenon in testin for components of compound Pavlovian conditioning. The point is, howeve that conditioned stimulation is typically compound in nature. If a dog i conditioned to a sound of 400 cycles at 40 decibels, for a duration of 25 sec. and is tested with a sound of 750 cycles, the decibel value has changed bu little and the duration not at all; hence, these unchanged, or relatively un changed, aspects of the conditioned stimulus become the carriers of the condi tioned generalization. The dog is not told what to watch for or what to watc *out* for, and does not tell us what he did watch or did watch out for; there i some advantage here in working with human subjects with whom one ca communicate a little better, but there other complications may arise.

A third type is related to the second type of generalization. I found, fo instance, in my human subjects the presence of conditioned generalization fro the sound to the sight of a metronome, even if the metronome was not see by them during the conditioning. Presumably, another common Pavlovia CR mechanism becomes operative, that of sensory preconditioning, or wha our Soviet colleagues call associative conditioning: namely, the establishe fact that when stimuli a_1 and a_2 are first repeatedly combined and later one o them is conditioned, the other also becomes conditioned in some way. Sovie experiments indicate that while this type of associative or sensory precondi tioning cannot be manifested in lower animals, it is quite common in dogs an apes and, of course, in man.

The fourth type of generalization may well be the most significant. I a thinking of generalization produced through common secondary proprioceptiv interoceptive, and orienting reflex conditioning, which recent Soviet exper ments indicate to be almost constant concomitants of primary exteroceptiv and primary sensory-interoceptive conditioning. These secondary condition

timuli and reactions are demonstrably less specific than the primary ones rom which they derive, and thus are natural agents of transfer or generalization. Beritashvili long ago demonstrated the significant role of secondary *torichnyye*) proprioceptive conditioning, and Anokhin has clarified the role f the orienting reflex in preparing and integrating conditioning. In my pinion, however, their work and thoughts must be extended to generalization: the fact that conditioning is, in United States terms, applied typically to a lass of stimuli and that secondary proprioceptive and interoceptive conditioned stimuli and reactions are class-building, class-compressing agents. In avlovian neurology one might say that typical conditioning involves not only he establishment of primary connections with the sensory analyzers of conditioned stimuli but also of secondary connections with the motor analyzer of hese stimuli, and that these secondary, motor-analyzer connections are, by heir very nature, less specific and more generalized than the primary sensory onnections. Or one might simply state that secondary proprioceptive and nteroceptive conditioning recodes and reclasses, in its own way, the primary onditioned information it receives; in this sense such conditioning is really a econd-signal system and verbal conditioning is a third-signal system.

Finally, my last type of nonirradiative generalization is that of conceptual eneralization, which pertains perhaps only—although not necessarily so—to uman subjects. In 1953 Volkova[4] in Krasnogorsky's laboratory reported on 13-year-old boy, conditioned to secrete a mean of 14 drops of saliva in 30 ec. to the sound of the word *khorosho* (good, well) and not to secrete to the ound of the word *plokho* (bad, badly, poorly). This subject would also salivate considerably when he heard such sentences as "The Soviet Army was ictorious" or "The Pioneer helps his comrades," but not when such sentences s "The Fascists destroyed many cities" or "The pupil was fresh to the teacher" ere pronounced. Presumably, the words *khorosho* or *plokho* were uttered or hought of by the subject when the respective sentences were heard. And seems reasonable to assume likewise the existence of some such mechanism n generalization. That is to say, a subject conditioned to one stimulus will nvoke, when another is presented, such concepts as "similar," "different," somewhat similar," "somewhat different," "very similar," "very different," nd so on, and these categorizing invocations will produce generalization and roduce it in different degrees. Studies of semantic conditioning certainly end general support to such a hypothesis. While my own specific results ith subjects instructed to invoke similar-different (or similar-dissimilar) ategories in their conditioned generalizations tests, as well as with subjects ho were merely asked to report awarenesses of such categories, are not clearut in delineating the role of categorizing in the generalization, one must reember that subjects are not always aware of their categorizing activities nd are not always able—or willing—to act according to instructions. As I entioned earlier, experiments with human subjects incur their own complications. Experimenter-subject and subject-experimenter communications are ot an enterprise of 100 per cent efficacy.

To summarize: I surely do not mean, however, to negate the role of neural radiation in generalization and the great significance of its direct investigaion; I merely point out the likely existence of nonirradiative mechanisms that

obviously must also be deciphered at the neural level. To ascertain the neural basis of any aspect of conditioning is not a simple task; to do so for conditioned generalization seems to me to be an even more complex undertaking.

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P. S. Kupalov (*Academy of Medical Sciences of the Union of Soviet Socialist Republics, Moscow, U.S.S.R.*): When I arrived in the United States I was very anxious to meet the scientists who are working in behavior. I do not know their literature very well, and it is difficult for me even now to understand it thoroughly; I think, therefore, that at this time I shall not attempt to answer all the questions put to me. I shall collect all the available material, think about it at home, and then I may discover that perhaps it will be necessary for me to repeat some experiments and see some of the facts in a new light.

I think that this publication will bring us closer together, but not at once: it will take some time to achieve full mutual understanding. Achievement of such understanding will be a good thing for science. I hope that Soviet students of the physiology of higher nervous activity will now take into account the investigations being made in the United States.

Before Pavlov published his second book he addressed all his pupils. He said then—I quote from memory—"For 25 years I have worked, and during nearly all this time I was doubtful of whether my way is right, of whether it is possible to study this complex phenomenon physiologically or not. I not only doubted but was tortured by the fact of my doubting. Now, after 25 years, I feel that my tortures are dissolving: you, my assistants, have collected a body of facts that prove to me that my basic premise was right."

That is what Pavlov said: that only 25 years of work had sufficed to make him certain he was right.

Science has now advanced to the study of more complex facts of brain activity—not necessarily based on behavior—but we Soviet workers explain from our point of view only those facts that are within the limits of our knowledge. That is quite natural. One may present such complex phenomena that it is impossible to explain them at present physiologically.

Therefore let us go on together, in close contact. I think that if we do, many new areas of understanding will be opened; and this, after all, was the purpose of our attending, in the United States, the conference upon which this monograph is based.

Part V. Psychopharmacology

INTRODUCTORY REMARKS

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This Pavlovian monograph is comprised of contributions from several groups. First, there are the papers of our honored colleagues from the Union of Soviet Socialist Republics. It is a great privilege to have been able to include work by these outstanding pupils and disciples of Pavlov, men who either knew Pavlov himself or participated in studies inspired by the genius of Pavlov. Many of Pavlov's pupils have already disappeared. Boris P. Babkin, who came to this country, has been dead about 10 years. Konstantin M. Bykov, whom we heard at the American Psychiatric Congress in San Francisco, Calif., in 1957, died two years ago. Leon Orbeli died about a year ago, and another venerable pupil, G. V. Volborth, this past summer. At the present time I think P. S. Kupalov is the eldest of the pupils of Pavlov. Among those represented in these pages who were working with Pavlov at the same time that I was are E. A. Asratyan and P. K. Anokhin. We were all together in Pavlov's laboratory in the 1920s.

We have evidence from the other Soviet contributors to this publication that Pavlov's influence continues in Soviet scientific developments today.

This monograph also includes papers by solid American investigators. Horace W. Magoun is one of those we recognize as a foremost physiologist in the development of science in this country.

However I was a little disturbed to hear about the division of the brain into the "Magoun brain" and the "Pavlov brain," because it seems to me that the brain works as one whole and that, despite the high achievements of both Magoun and Pavlov, the brain is not going to refer to Magoun or Pavlov in order to know what to do. Although this division was not meant to be taken too seriously, it is a dichotomy that will prove to be an approach to the same problem from two different aspects, both of which are equally true.

It is likewise disturbing to hear about a division of the world into two opposing halves. Irrespective of any political affiliation, I think it is inevitable that sooner or later we must come to one world, just as we must to one brain, in order to avoid mutual destruction. Let us hope we can accomplish this with the preservation of the rights of the individual.

We have also in this monograph some of the United States devotées of Pavlov. Among these is Howard Liddell, who has been a pioneer in this field since the early 1920s. He was one of the first, if not the first, to transplant the conditional reflex of Pavlov to United States soil.

In addition, we have the "grandchildren" of Pavlov, people who have worked with those who have worked with Pavlov. Knowing many of these personally, I have reason to feel that among them we shall find people who are real followers of Pavlovian principles and who, by using strictly objective methods, will do a great deal to advance this knowledge. It was in the dawn of our

professional lives that Liddell and I met in the 1920s in Pavlov's laborator When Liddell and Kupalov and I were in Leningrad discussing Pavlovia principles, we did not foresee meeting one third of a century later in the pages to register the advance of his principles.

It is of interest that Liddell represents a kind of inquiring spirit that difficult to find at the present time because of altered circumstances. The are both advantages and disadvantages to the plutocratic era in which w live in the solid support and underwriting of science. Liddell came to th Soviet Union, just as I did, in the 1920s, as an unsubsidized pioneer to inves gate Pavlov's work.

I heard Anokhin make a parallel statement at his 60th year jubilee in th Soviet Union two years ago: that the young Soviet scientists enjoy a degree support that was unknown at the time that Anokhin was working in Pavlov laboratory. What has happened in the Soviet Union has also happened some extent in the United States and in other parts of the world. As Pavlo said, we must accept the responsibility put upon us of advancing science wi the increased support that government and other agencies are giving to u we scientists who were once paupers but are now princes. Let us hope th this change will carry with it the sense of *noblesse oblige*.

Pavlov began his work (which some of us are likely to forget because of t overshadowing interest, at the present at least, in the conditional reflex) as physiologist of digestion, for which he received the Nobel Prize in 1903. H also did very important work on circulation in the 1880s. For those who a interested in circulation, it would be a great advantage to go back and rea Pavlov's descriptions of his experiments, because many of these have bee forgotten. It was Pavlov who, with W. H. Gaskell, discovered the "trophi nerves to the heart. Pavlov does not usually get the credit for this, not b cause of any desire to discriminate against Russian science but because of t paucity of contacts with that country in those days and the difficulty of t Russian language.

As an example of this lack of contact: when I went to the Soviet Union wi the American Relief Administration in 1922, Pavlov's obituary had been pu lished in the Encyclopedia Britannica, reporting that he died in 1916. Actual Pavlov outlived his obituary by 20 years.

In his work on circulation, Pavlov measured blood pressure directly; h skill in working with the chronic animal we do not see duplicated today, ev in the most advanced cardiovascular laboratories.

In the early part of his career, Pavlov also worked in pharmacology with th famous Russian clinician Botkin. Pavlov made some important suggestio regarding pharmacology that, it seems to me, have not been given the atte tion they deserve. He divided his dogs into types and found that there was relationship between the action of certain drugs and the type of dog. He d this especially with bromides and with caffeine, finding that the dose shou be regulated to the type of the dog; he found, furthermore, that these dru had an entirely different effect on different animals depending upon wheth the dog was of excitatory or inhibitory temperament.

The advance of psychopharmacology at the present time has been due large to the foundations that Pavlov laid for our work in neurophysiology and neur

pharmacology through the application of the conditional reflex. It is because of this that we are able, in animals, to see the effect of drugs and to know what really is the placebo effect; what is the effect of the experimenter on the animal; what is the real effect of the drug.

We also see another application of the conditional reflex in electrophysiology, which is being undertaken by H. H. Jasper and others. In my laboratory, my collaborators and I have developed, especially, cardiovascular conditional reflexes that enable us to make a study of the influence of the environment, of stress, and of psychogenic factors on cardiovascular normal physiology, as well as on the pathology of the cardiovascular system.

We are well aware of the chemical advances made in psychopharmacology. Zakusov tells us about some of them in these pages. In the United States a large amount of work is devoted to this subject: for example, Heath in his work with schizophrenics and Woolley, Page, and others in the development of serotonin.

With all due respect to those who are working on the chemical aspects of behavior and with commendation for the enthusiasm they have displayed—necessary in any scientific endeavor—at the present time it seems that we do not have a rational basis for a real biochemical explanation of neurotic development. This is not because of the lack of excellent biochemical work going on in this field; I think it is because knowledge of the brain—of different parts of the brain—that really constitutes the basis for neurotic development has not kept pace with the biochemical research; we need to know more in this field of neurophysiology before we can intelligently apply biochemical principles in the way they should be applied. The fact that biochemistry deals with items too close to the molecular level may, as pointed out by A. Szent-Györgyi, be another reason.

In the future, there will undoubtedly be a solution of many of these problems in the control of pathological behavior through biochemistry. Hitherto it has been largely a question of hit-and-miss, of finding a drug by accident that affects behavior, rather than—as perhaps the work of Kety, Heath, Woolley, Page, Zakusov, and others will make possible—by approaching psychopathology from a rational biochemical basis.

Pavlov's development of the conditional reflex was strictly a Russian development, beginning perhaps with the father of Russian physiology, Ivan Mikhailovich Sechenov, who wrote on reflexes of the brain and laid down on a theoretical basis in 1863 (the book was published then) many of the principles that Pavlov later elucidated in the laboratory.

It was Pavlov in our era who brought down to earth and into the laboratory the so-called psychical life. His attitude toward this was expressed in his statement that he deemed the language of facts the most eloquent. This does not mean that Pavlov did not see the advantage of theory. He devised many theories himself. He employed theory, I think, in a way that is the most useful to science: that is, he constructed an hypothesis, went to the laboratory, and made observations to find out whether his theory held or not; he was the first to discard his theory when he found that it did not hold. He stated, with some regret, in regard to the discovery of secretin by Bayliss and Starling which was contrary to his theory of the control of pancreatic secretion entirely

through the nerves): "Of course, they are right; we cannot always claim that our theory is the only right one."

Moreover, we are likely to forget Pavlov as a person because of the obscurity of the facts of his life. We are apt to forget Pavlov's courageous, forthright nature, both personal and professional: he always stood for what he considered the truth. He had devoted his whole life to science, and his attitude was summed up in his last will and testament, in which he said that one's whole life is not enough to devote to science; "even if one had two lives to give, these would not suffice."

I think we are now beginning—to the great satisfaction of those who have known Pavlov, who know his work, who feel that his principles are extremely important in the study of our higher nervous activity, of our behavior both normal and abnormal—to see a prophesy of H. G. Wells come true. In the 1920s Wells wrote that Pavlov's fame would grow with the ages, and that within 100 years he would be much more important than he was at that time during his life.

PSYCHOPHARMACOLOGY, THE PATHOPHYSIOLOGY OF HIGHER NERVOUS ACTIVITY, AND CLINICAL PSYCHIATRY

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Regardless of their adherence to particular schools, psychiatrists of every country in the world are directing their research efforts toward discovering the internal basis, or essence, of the external manifestations of psychoses—in other words, the pathogenesis of these manifestations—in order that they may continually improve the treatment of patients. This is the aim of those psychiatrists who are developing the psychological approach to psychiatry; it is the aim of clinical psychiatrists; and it is equally the aim of those psychiatrists who adopt a physiological, electrophysiological, biochemical, histopathological or, recently, a psychopharmacological approach.

Contrary to the opinion of certain of the most orthodox representatives of each of these approaches (or methods, or branches), none of these approaches is in a position to discover the essence of psychosis by itself. The final results of each method of investigation taken alone will always be one-sided. What is more, not one of the existing approaches to psychiatry has reached the limit of its possibilities; they are all still in their infancy.

Despite a widespread opinion to the contrary, the clinical method (or the phenomenological method, as American and English psychiatrists call it) also has not exhausted its possibilities. The more we learn about the pathogenesis—the internal latent pathological patterns—of psychoses, the more perfect our knowledge of their outward clinical manifestations will become, and the more successful our diagnosis and, accordingly, our immediate therapeutic practice.

The importance of each of the approaches (or trends, or methods) mentioned above has constantly changed, depending on the particular way in which natural science has progressed. As science has developed, first one approach and then another has occupied the dominant position. Thus, at the beginning of the 19th century the dominant approach was the psychological one (Esquirol, Heinroth, and Ideler).[1] Under the influence of Charles Darwin's ideas, the evolutionary approach took over (Griesinger, Maudsley, Ribaud, and Jackson). Later, the psychophysical and anatomic-physiological approach became dominant (Meynert, Wernicke, and Wundt), and then came the clinical approach (Kahlbaum and Kraepelin).[1] Now psychopharmacology is beginning to occupy an increasingly dominant place.

When one approach becomes dominant, all the other areas of psychiatry are stimulated, reorganized, and enriched in the corresponding direction, and the result is an all-around investigation of both the manifestations and the pathogenesis of psychoses.

In this way psychopharmacology, in its rapid development, has influenced Pavlovian investigations in the area of the pathophysiology of higher nervous activity. Pavlov introduced pharmacological treatment with prolonged sleep and with bromine and caffeine, in order to learn more about the basic nervous

processes he was studying—namely, excitation and inhibition—and to obtai better control over them.

The subsequent development of psychopharmacology not only has confirme Pavlov's view of the basic nervous processes responsible for conditioned-refle activity (this is reflected, for example, in the principle used to classify psycho tropic agents), but has also opened up remarkable opportunities for furthe investigation of these processes.

Psychopharmacology has given us equally extensive opportunities for stud of the energetics of the subcortex (reticular substance) and the physicochemica substrate of nervous activity. "Only by studying the physicochemical proc ess that is occurring in the nervous tissue will we obtain a genuine theory c all nervous phenomena; the phases of this process will provide us with a com plete explanation of all the outward manifestations of nervous activity, th sequence in which they appear, and the connections between them," Pavlo wrote.[3]

To put it briefly, at the present time our most effective means of investigat ing the fundamental problems of the material substrate of life and the ene getics and regulation of metabolic processes (S. Ye. Severin, cited by Engle hardt[12]) in the area of psychopathology is the utilization of psychotropic agent

In addition to contributing to the pathophysiology of higher nervous activit and the biochemistry of the brain, psychotropic agents have exerted an unques tionable influence on the development of clinical psychiatry and its correlatio with the pathophysiology of the brain.

For example, by comparing the effectiveness of chlorpromazine therapy c patients in various stages of paranoid schizophrenia—or more correctly, i various segments of its developmental stereotype (paranoial, paranoid, para phrenic, and secondary catatonia*)—we have been able not only to exten our knowledge of the clinical aspects of this disease but also, to some extent, t correlate its psychopathological manifestations more precisely with particula features of the disturbance of higher nervous activity.

As shown by a clinical investigation of 659 patients with paranoid schiz phrenia, the disease usually begins with one of three types of disorder: th paranoial type, obsessive symptoms, or depersonalization. It is suppose that these disorders are based on a pathological inert excitation of connectio predominantly of the second signal system, with derangement of their inte relation and with a predominance of the second signal system over the firs and of the cortex over the subcortex.

* By the "paranoial" state we mean the presence of interpretative, systematized delusio without hallucinations and symptoms of psychic automatism. Systematized delusions ar circumstantiality of thought establish the clinical picture of psychosis.

The "paranoid" state is characterized by systematized delusions with content of vario sorts, delusions of physical influence, hallucinations, and a variety of symptoms of psych automatism.

The "paraphrenic" state consists of these disorders, together with fantastic dreamli delusions of grandeur and power.

In "secondary catatonia" catatonic disorders exist side by side with paranoid-hallucinato or paraphrenic disorders. The transition of paranoial disorders into paranoid and then in paraphrenic, as the psychosis develops, was first described by Magnan.[16] To be sure, t course of paranoid schizophrenia very often deviates considerably from that described b Magnan, but the electroencephalographic investigation presented in this paper was carri out on patients in whom the disease had followed the classic course.

To investigate this correlation, we undertook parallel studies with the toposcope (electroencephaloscope) and with pharmacological tests (pipradrol*), in addition to our clinical study.

The bioelectric mosaic of the cerebral cortex was investigated with the electroencephaloscope described by M. N. Livanov and V. M. Anan'yev,[2] which makes it possible to record bioelectric potentials from 50 points on the cerebral cortex.

This instrument works on the principle of electronic commutation, by which impulses coming from all the electrodes are amplified sequentially by a single common three-cascade impulse amplifier. The sweep circuit is such that 50 illuminated spots appear on the kinescope screen, arranged in five rows. Below these spots on the screen there are 50 columns, each of which corresponds to a particular spot. In turn, each spot and each column correspond both in position and in number to a particular electrode on the patient's head.

The 50 electrodes are all fastened to the patient's head, in five rows with 10 electrodes in each row. The first row of electrodes is situated 4.5 cm. above the superciliary arches, and the fifth is at the level of the external occipital protuberance. The other rows are spaced at equal distances between them. The designated order of both the electrodes and the spots on the screen is from left to right and from top to bottom. The first (upper) line corresponds to the first row of electrodes (forehead), and the fifth (lowest) line to the last row (occiput). The first five spots on the left of each row (1 to 5, 11 to 15, 21 to 25, 31 to 35, and 41 to 45) correspond to the left hemisphere, and the five spots on the right (6 to 10, 16 to 20, 26 to 30, 36 to 40, and 46 to 50) to the right hemisphere.

A change in the potentials beneath a particular electrode is accompanied by a change in the intensity of the corresponding spot and a change in the height of the column. The latter permits a quantitative determination of the potential change at the corresponding point. Before the examination of the patient, the heights of all the columns are set equal to each other and, consequently, so are the intensities of all the spots. Variations in the bioelectric potentials change the intensity of the spots and, correspondingly, the height of the columns. The potential of each electrode (the region of the cortex under the electrode) is determined in relation to the mean potential of all the electrodes (the mean cortical potential).

An increase in the negative potential under the electrode is accompanied by an increase in the intensity of the spot that belongs to it and an increase in the height of the column. A positive potential has the opposite effect. Because of the anelectrotonic nature of inhibition, regions with a positive potential correspond to zones of cortical inhibition. Negative potential regions correspond to zones of cortical excitation.

The time course of the spatial distribution and changes in the bioelectric activity of the cerebral cortex are observed visually on the kinescope screen and are simultaneously recorded on a motion picture film (24 frames per second).

Biolectric activity was studied in the resting state (background record),

* Marketed in the United States as Meratran.

during functional loading (application of an intermittent light of increasing brightness or of sound stimuli), and also after the administration of pipradrol in increasing doses of from 1 to 3 mg.

During the examination, patients lay in a horizontal position in a shielded, darkened, and soundproof room.

In healthy individuals, the bioelectric mosaic is characterized by a dynamic quality: it changes every 0.04 to 0.08 sec., the mosaic picture is rarely repeated and is distinguished by its variety. Foci of increased activity arise at various points on the cortex, with an intensity of not more than 100 to 150 microvolts; usually, they do not recur at the same points.

Waves of cortical activity ("overflows")—changes in the intensity (potential) of a large number of spots in any one region, with a synchronous potential change of the opposite sign in another region (for example, a rise of negativity in the frontal lobe accompanied by the appearance of positivity in the occipital lobe)—are ordinarily infrequent. Under the influence of a photic stimulus, the bioelectric mosaic changes: the alpha rhythm disappears, the numerical relationships change, foci of elevated activity appear, and diffuse activity is either elevated or reduced (FIGURE 1).

Compared to electroencephalography, electroencephaloscopy provides information of a more graphic sort about the spatial distribution of the brain's bioelectric activity, and about the changes in this activity with time.

The characteristics of these two methods of recording the bioelectric activity of the brain, electroencephalography and electroencephaloscopy, are best illustrated by a comparison of the following data from a patient with photoepilepsy.*

Three electroencephalograms were recorded with an Al'var system polygraph (FIGURE 2). The first of these shows the changes occurring in the brain potential variations under the influence of an interrupted photic stimulus with a flicker frequency of 4/sec. Before the application of this stimulus, the record shows a more or less clear-cut spindle-shaped alpha rhythm. Under the influence of the photic stimulus the alpha rhythm is depressed. In the frontal lobes and, to some extent, in the temporal lobes, variations connected with oculomotor reactions appear.

In the second electroencephalogram, changes in the potential variations occur under the influence of a photic stimulus with a flicker frequency of 12/sec. During the application of the stimulus, paroxysms of pathological activity develop in the form of a spike-slow wave complex in all leads.

In the third record, under the influence of a light stimulus with a flicker frequency of 15/sec., the patient suffered a petit-mal seizure. At the same time the pathological spike-slow wave complex became more prolonged and intense.

Four pairs of motion picture records (grouped vertically), obtained with the electroencephaloscope, are shown in FIGURE 3. The first two (*a*) were taken while the patient was resting, before the photic stimulus was applied: diffuse activity is seen.

* These data of F. A. Leybovich, a co-worker in the academic group, were obtained in the laboratory that she occupies jointly with M. N. Livanov. These data are cited in an article by I. M. Savich.[13]

In the next two records (*b*), made upon the application of a photic stimulus with a frequency of 12/sec., we see a wave of cortical activity, traveling in the frontal-to-occipital direction, with a focus of elevated negativity in the parieto-occipital region of the right hemisphere.

In the third and fourth pairs (*c* and *d*), under the influence of a photic stimulus with a flicker frequency of 15/sec., one focus of elevated activity first

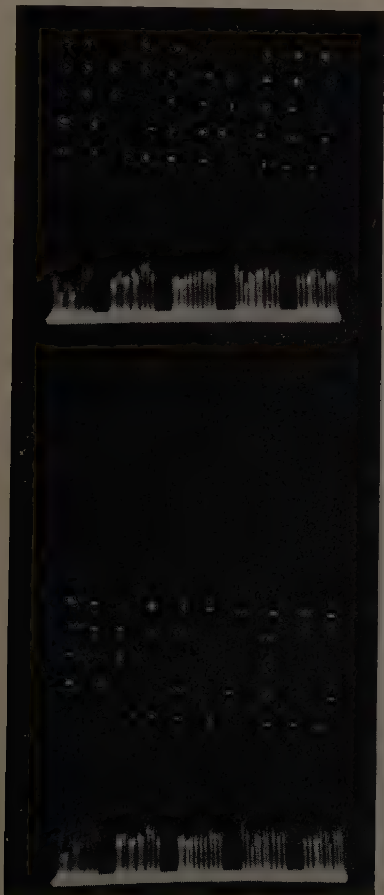

FIGURE 1. A normal bioelectric mosaic.

develops in the parieto-occipital lobe, and then multiple foci are seen in the occipital lobe. After these foci appeared, the patient suffered a grand-mal convulsive seizure.

In patients with paranoid schizophrenia,* the dynamic quality of the bioelectric mosaic was greatly reduced at all stages in the development of the

* The investigations of schizophrenia described below were performed at the clinic of the TsIU (Central Institute for Advanced Training of Physicians) by N. Ya. Belen'kaya, under the supervision of M. N. Livanov, in their common laboratory.[4]

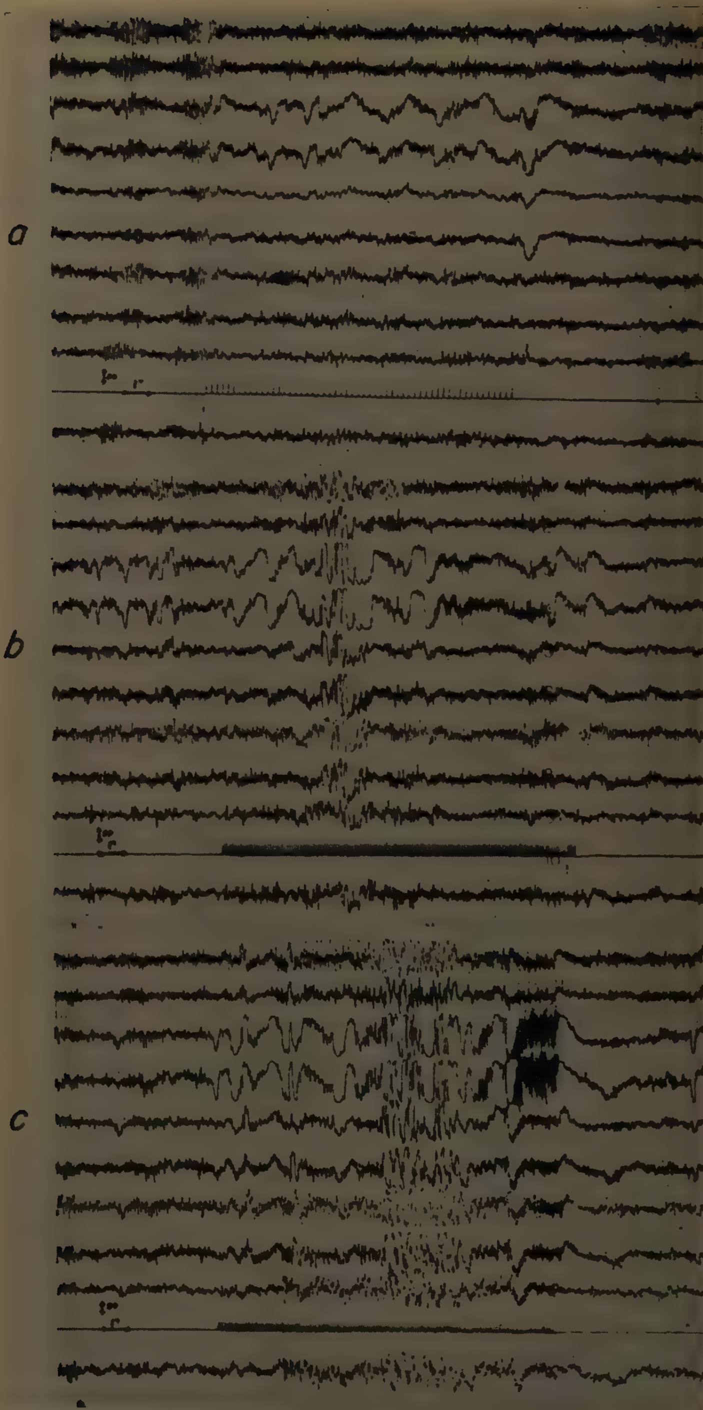

FIGURE 2. Electroencephalograms of a patient with photoepilepsy.

FIGURE 3. The bioelectric mosaic of the same patient.

disease: no clear-cut changes were seen over a period of 0.1 to 1.5 sec., and such changes as did arise in the mosaic were characterized by extreme uniformity (FIGURE 4). The bioelectric activity consisted of continual waves of activity of a single type. When a light stimulus was applied (in 364 out of 428 examinations), no changes were observed in the mosaic.* In addition, when changes occurred in the activity of the bioelectric mosaic, each individual

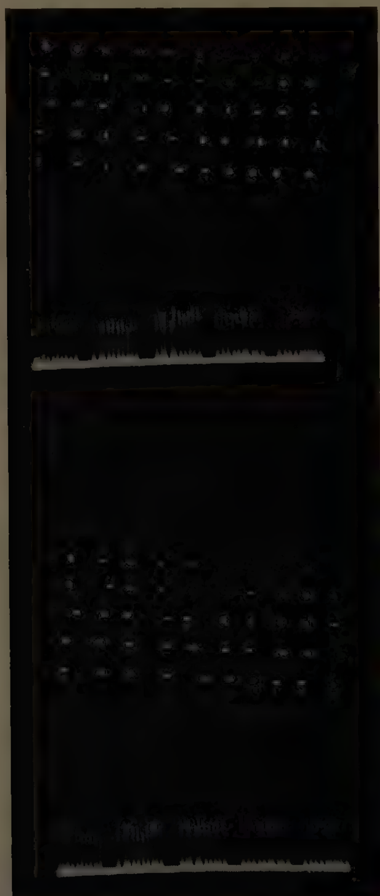

FIGURE 4. Bioelectric mosaic of patient with paranoid schizophrenia.

period of development of paranoid schizophrenia (paranoial, paranoid, para-phrenic, secondary catatonia) had its own characteristic features and its own reaction to the administration of pipradrol.

For example, in the majority of the patients examined in the paranoial state the bioelectric mosaic was characterized by inactivity, with infrequent waves of small intensity, spreading from the forehead to the occiput; inert foci o

* The characteristics of the change that occurs in the bioelectric mosaic, recorded with the electroencephaloscope in schizophrenic patients, were first described by N. A. Gavrilova.

hyperactivity were not ordinarily seen. Upon the application of a light stimulus, a change in the mosaic was observed much more often than in all other forms of schizophrenia. In the majority of these patients, 20 to 50 min. after the administration of pipradrol, usually in a dose of 3 mg., the dynamic quality of the bioelectric mosaic was clearly increased, and in many patients foci of

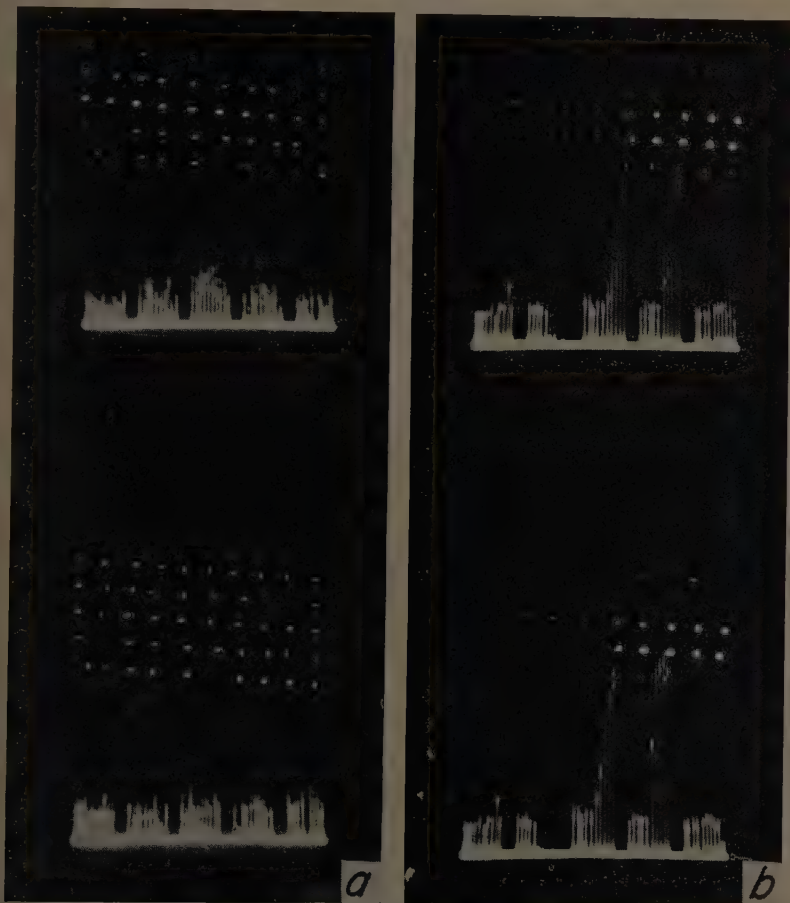

FIGURE 5. Background bioelectric mosaic of patient in the paranoial state (*a*), and mosaic of patient in the paranoial state under the influence of pipradrol (*b*).

hyperactivity developed or existing foci were intensified (up to 200 μv), as shown in FIGURES 5*a* and *b*.

In contrast to schizophrenic patients, pipradiol usually produced not focal, but diffuse, elevation of activity in healthy individuals (FIGURE 6).

In patients in whom pipradrol produced an elevation of bioelectric activity with the formation of foci (in contrast to patients who were nonreactive to pipradrol), subsequent treatment with chlorpromazine (Aminazine) resulted in the onset of a remission. This indicated a direct proportionality between

the degree of retention of excitation processes, lability of basic nervous proc-esses, and effectiveness of therapy employed.

This type of relationship between the pathological inertness of the basic brain processes and the effectiveness of therapy illustrates general pathological principles. I. V. Davydovsky writes in this connection: "Every process in nature, including every disease process, *is relatively stable*; it has a number of

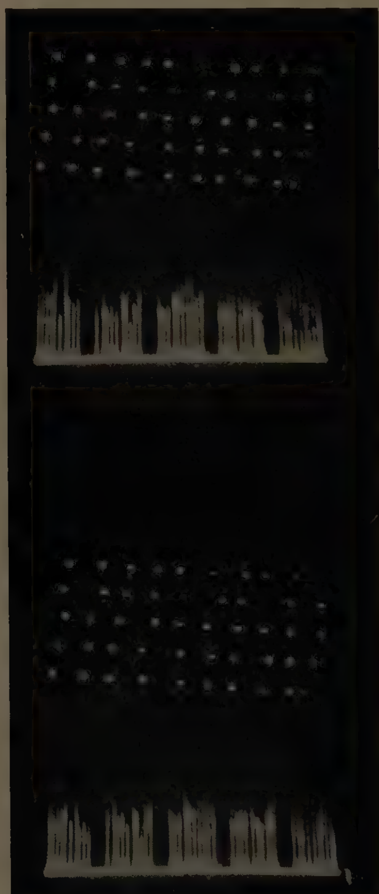

FIGURE 6. Bioelectric mosaic of normal subject under the influence of pipradrol.

steps that determine its development." According to Davydovsky, recovery or a change in the course of the disease, is achieved only when it is possible to influence one of these steps, or to disrupt several steps in the pathologica process.[6]

This relationship between the degree of pathological inertness and the effec tiveness of chlorpromazine therapy emerges more strikingly in the later stage of schizophrenia.

In the hallucinatory-paranoid period of development of delusional schizo

phrenia, the bioelectric mosaic was far more lifeless and inert than in the paranoial stage. Changes in the pattern were seen less frequently; the pattern also changed less often under the influence of the light stimulus. In contrast to the paranoial state, during this period of development of paranoid schizophrenia inert foci of excitation (up to 250 μv) were often observed, even before

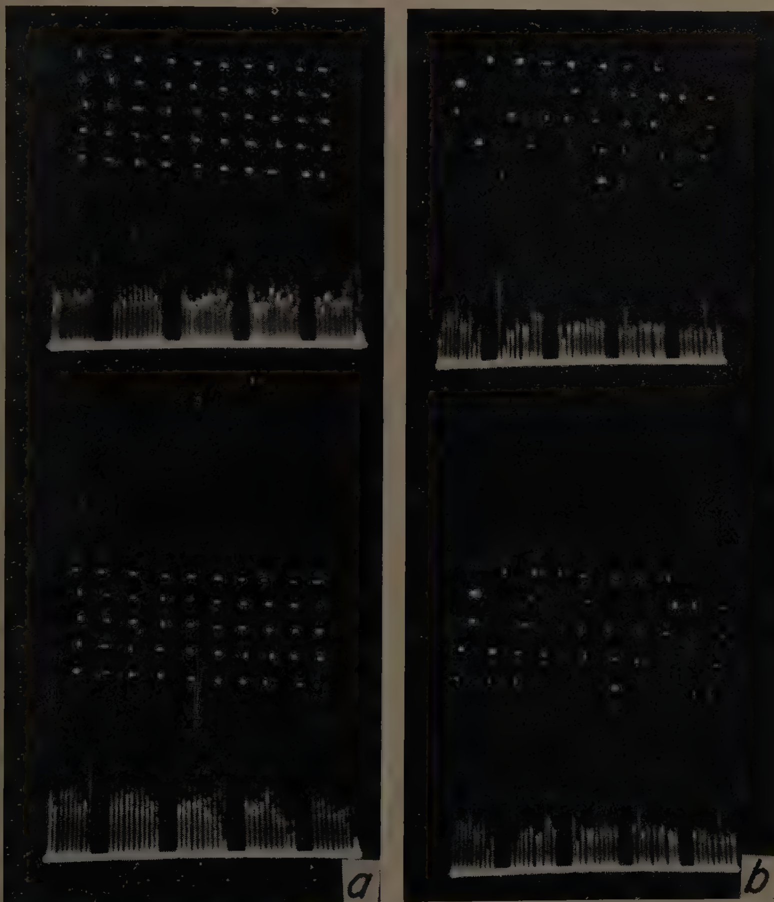

FIGURE 7. Background bioelectric mosaic of patient in the paranoid state (*a*), and mosaic of patient in the paranoid state under the influence of pipradrol (*b*).

administering pipradrol, thus creating a picture of asymmetry between the hemispheres.

After pipradrol, new foci of increased activity appeared in the majority of patients, and existing foci were greatly enhanced (up to 300 μv). As a rule, the clinical manifestations of delusions were sharply increased at this time, as were the symptoms of psychic automatism. In some examinations, the bioelectric mosaic began to react to the photic stimulus where it had not done so previously (FIGURES 7*a* and *b*).

In these patients, just as in the paranoial patients, the degree of effectiveness of chlorpromazine treatment corresponded to the degree of reactivity of the bioelectric mosaic to the administration of pipradrol to the organism, that is to the degree of mobility of the basic nervous processes. I also call your attention to the great complexity of the bioelectric mosaic of the cerebral cortex of patients with hallucinatory-paranoid schizophrenia, as compared with patients suffering from paranoial schizophrenia. This polymorphism revealed the more complex pathogenesis of this stage of the disease, which was correlated with the greater complexity of the clinical picture of the paranoid stage as compared with the paranoial.

Changes in the bioelectric mosaic during the paraphrenic period of development of paranoid schizophrenia and in secondary catatonia were characterized by increasing complexity and inertness, in comparison with the preceding stages.

The presence of stable foci of hyperactivity (up to 200 μv) distinguished the bioelectric mosaic of the cerebral cortex of most paraphrenic patients before the administration of pipradrol. After various intervals of time, these foci uniformly became very sluggish. The duration of waves of activity became as great as 1.5 sec.; these usually spread from the forehead to the occiput, but there were also fragmentary interhemispheric waves that spread from one hemisphere to the other (FIGURES 8*a* and *b*).

The bioelectric mosaic usually did not change in response to the administration of pipradrol.

In patients with catatonic disorders that had arisen during the course of paranoid schizophrenia ("secondary" catatonia), the bioelectric mosaic was characterized by still greater complexity and inertness. Before administration of pipradrol the cortical mosaic was usually characterized by the presence of multiple foci cf hyperactivity (with an intensity of up to 300 μv), which arose at the same points throughout the entire investigation (a "constellation"—a periodic repetition of the character and spatial distribution of cortical potentials of processes—that is, a stereotype of these potentials). Besides this, frequent multiple waves of activity of entirely different tendencies were observed. In approximately one half of the patients, administration of pipradrol did not alter the cortical biomosaic, and in the other half it led to a decrease in activity (paradoxical reaction) (FIGURES 9*a* and *b*).

Chlorpromazine therapy had little or no effect in patients with either paraphrenia or secondary catatonia.

Naturally, the correlation we have cited between the characteristics of the clinical manifestations of psychosis, the bioelectric mosaic, and the reactivity of the bioelectric mosaic to the administration of pipradrol is especially preliminary and very general. Still, it reflects to some degree the material substrate of the psychopathological manifestations of the brain process and its dynamics.

In dynamic clinical studies of patients with paranoid schizophrenia, it has been established beyond any doubt that, as the disease develops, simple ("lesser") psychopathological syndromes gradually become more and more complex (or "greater").* Thus the initial manifestations of paranoid schizo

* The concept of "lesser" and "greater" syndromes is that of V. Kh. Vasilenko.[7]

phrenia (in the form of systematized interpretative delusions, or various types of compulsiveness or, finally, symptoms of depersonalization) are increasingly complicated by the appearance of new disorders as the disease develops: a sense of being possessed, or influenced, by the "symptom of openness," pseudo-hallucinations, and other diverse phenomena of psychic automatism. The clinical picture of psychosis becomes the hallucinatory-paranoid one. As the

FIGURE 8. Background bioelectric mosaic of paraphrenic patient (*a*), and mosaic of paraphrenic patient under the influence of pipradrol (*b*).

disease subsequently progresses the complication deepens; the hallucinatory-paranoid state is joined by dreamlike fantastic delusions of grandeur (the paraphrenic stage). In many instances, as the disease develops, a new complication follows: in addition to the hallucinatory-delusional state, catatonic disorders develop.

This increasing complexity also corresponds to data from the pathophysiology of higher nervous activity, which indicate that as a result of a long-standing focus of inert excitation, an ultraparadoxical phasic state arises (the basis of

the syndrome of psychic automatism). Thereafter, as a result of inductive inhibition or exhaustion, protective inhibition gradually develops, apparently in the cells of the cerebral cortex, and then spreads to individual signal systems or analyzers (the physiological basis of dreamlike delusions and the catatonic state).

FIGURE 9. Background bioelectric mosaic of patient with secondary catatonia (*a*), and mosaic of patient with secondary catatonia under the influence of pipradrol (*b*).

All of this taken together, however, illustrates the general pathological principles of the development of any disease: a continuously developing chain reaction of the organism, with an ever-greater magnification of the pathogenetic links of which the pathogenesis of the disease is composed.

The development of this pathological chain reaction occurs automatically in the presence of actively harmful conditions. As paranoid schizophrenia develops, the paranoial or obsessive state inevitably is transformed (on the principle of the self-developing syndrome of the French psychiatrists) into the

paranoid-hallucinatory state, and then into the paraphrenic state and secondary catatonia. "From the physiological standpoint," writes I. V. Davydovsky, "this automatism is a complex chain reaction, which develops like any stereotype in a definite rhythm, with definite biochemical, morphological, electrophysiological, immunological, and other signs. . . . Theoretical analysis of pathological processes at the modern level permits us with a high degree of accuracy to determine the individual links of the automatically evolving chain reactions, which usually take the form of symptom-complexes or syndromes. Among such stereotypic reactions we might include fever, Selye's adaptation syndrome, the antigen-antibody reaction, the hepatorenal syndrome, shock, and many others."[8]

The increase in the relative stability and inertness of such automatic chain reactions as a disease progresses is illustrated in the area of the psychoses by the bioelectric reaction of the brain to pipradrol and by the effectiveness of chlorpromazine treatment.

It is interesting to note one feature of these automatically evolving pathological chain reactions. At the onset of recovery due to chlorpromazine therapy, the process makes an orderly change in a direction opposite to its own development. As the remission develops, symptoms that have arisen most recently disappear first, and the initial symptoms disappear last. The psychosis ends with those disorders with which it began. At the onset of the remission, complex symptoms are replaced by less complex symptoms, and then by simple ones. In incomplete recovery, simple symptoms often remain during the remission as residual disorders (compulsive symptoms, paranoial changes, or an asthenic state).

This characteristic illustrates a principle of evolution: the disorders that arise first are also the most organized and, consequently, the most inert links in the pathogenesis of the disease. The disorders that arise later are less highly organized, less thoroughly automatized, and less inert. During treatment they disappear first.

As a result of chlorpromazine therapy of paranoid schizophrenic patients, the bioelectric mosaic gradually becomes normal. Foci of increased activity disappear, waves of activity are reduced, and cortical activity is gradually increased (FIGURE 10*a*). However it should be mentioned that, despite continuing remission, in some patients the earlier pathological changes are once again detected at electroencephalographic examination, although they are less marked.

The existence of pathological changes in the bioelectric mosaic of the brain (FIGURE 10*b*), despite the absence of changes in the clinical picture of a continuing lucid interval in the course of schizophrenia, can be understood in the light of A. D. Speransky's concept of the presence of trace effects in the central nervous system, despite the disappearance of external manifestations of disease.[9] In many patients this view has been confirmed by the onset of a schizophrenic relapse under the influence of various nonspecific stimuli ("the second shock"), such as psychogenic traumas, overwork, and commonplace infections.[10]

It should be pointed out that the increasing complexity of the bioelectric mosaic, as schizophrenia develops, is generalized. Predominance of various local changes, depending on the particular characteristics of the syndrome, is

very irregularly recorded. It can be said, with many qualifications, that in the hallucinatory-paranoid state foci of elevated activity arise more often in the area of the temporal lobe; in the catatonic state they arise in the motor cortex.

FIGURE 10. Bioelectric mosaic of schizophrenic patient during chlorpromazine therapy (*a*), and mosaic of schizophrenic patient during remission occurring after chlorpromazine therapy (*b*).

The existence of a correlation between the complexity of the clinical picture of psychopathological syndromes and the diversity of disorders of the bioelectric mosaic of the cerebral cortex is also confirmed by comparison of the data of electroencephaloscopic examination of patients suffering from cyclothymic depression (FIGURE 11) and depressive-paranoid schizophrenia (FIGURE 12), during treatment with iproniazid (isonicotinic acid hydrazide, Iprazid).

The bioelectric mosaic of the classical depressive phase of the manic-depressive psychosis, prior to treatment with iproniazid, was characterized by the

following features.* Besides a diffuse reduction in bioelectric potential variations and reactivity, almost no other changes in activity were encountered. The bioelectric potential variations were symmetrical. Alpha waves were recorded in the occipital lobes and, in some instances, everywhere. An inter-

Figure 11. Bioelectric mosaic of patient with cyclothymic depression.

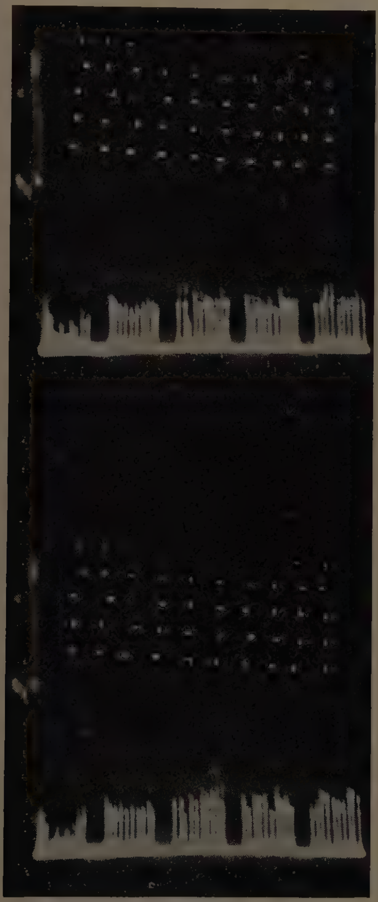

Figure 12. Bioelectric mosaic of patient with depressive-paranoid schizophrenic depression.

mittent light stimulus, or the application of sound stimuli, was not accompanied by any clear-cut changes in bioelectric activity.

After 10 to 12 days of treatment with iproniazid, and simultaneously with clinical improvement of these patients, a gradual animation and a heightening of diffuse activity (sharp spikes in the electroencephalographic record) were usually observed, chiefly in the temporal lobe, sometimes on the right hemi-

* These investigations were carried out by F. A. Leybovich, a co-worker in the academic group, under the supervision of M. N. Livanov, in their common laboratory.[11]

sphere and sometimes on the left, and often with uniform repetition (constellation). When stimuli were applied, depression of the alpha rhythm was observed. In the vast majority of patients there was increased reactivity.

The disturbances in the bioelectric mosaic were more diverse in all patients with depressive-paranoid schizophrenia, a syndrome that is clinically much more complex than the uniform syndrome of cyclothymic depression. Unlike patients with classical depression, those with delusional depression displayed asymmetry of activity between corresponding points on the two hemispheres and the absence of a distinct alpha rhythm in the occipital cortex, in addition to a diffuse reduction of mobility and reactivity. In individual patients, periods of reduced activity in the frontal lobes were noted from time to time. Existing foci of increased activity were of a low intensity and inert in character. Application of stimuli either was accompanied by changes in activity or produced a certain amount of intensification of pathological signs (deepening of asymmetry, increase in frontal lobe positivity, and enhancement of inert foci of hyperactivity).

As a result of iproniazid treatment, an increase in the pathological forms of activity was noted in all cases of depressive-paranoid states: there was a marked intensification of the zone of positivity in the frontal lobes, and of foci in the temporal lobes. In one case, multiple high-amplitude foci of hyperactivity developed in the motor cortex, as is the case in epileptic patients.

Clinically, improvement failed to occur in every case of depressive-paranoid depression. The condition of two patients deteriorated as a result of the intensification of delusions. On the other hand, when patients with cyclothymic depression were treated they either recovered or showed great improvement.

Thus to the clinically uniform, simple syndrome of cyclothymic depression there corresponds a uniform change in bioelectric activity, reflecting diffuse inhibition of the cortex and subcortex, with hindrance of the formation of new cortical connections and retention of processes of internal inhibition. The restoration of normal conditions under the influence of a neurotonic agent testifies to the comparative simplicity of the pathogenetic links.

On the other hand, the clinical complexity of the depressive-paranoid syndrome corresponds to the polymorphism of the changes in the bioelectric mosaic, which reflects the diversity of the disturbances in the activity of the higher nervous system. In these conditions, against the background of inactivity and increased inhibition of nerve cells, the formation of ineffectual points and foci of inert excitation is observed. The correspondence between the clinical polymorphism of the syndrome and the complexity of the links in the pathogenetic chain are confirmed by the fact that the neurotonic iproniazid is either indifferent or causes the patient's condition to deteriorate.

Modern psychotropic agents permit us to reduce a complex syndrome to a simple one by influencing one or more pathogenetic links.

We see this every day in the chlorpromazine treatment of patients with periodic depressive-paranoid schizophrenia.* Often, in treatment with this agent, patients' delusions, verbal illusions, and bustling excitation vanish, but

* Data of T. N. Morozova, a co-worker in the academic group.[14]

the depression remains and is sometimes even intensified. The picture of psychosis becomes uniform, and at times is hard to distinguish from cyclothymic depression. It is also interesting to note that in individual patients a later attack, following treatment with chlorpromazine, took the form of agitated depression without delusions or hallucinations.

On the other hand, treatment of depressive-paranoid schizophrenia with Tofranil often leads to a different, even opposite, simplification of this complex syndrome. In such cases, the depression disappears and the delusions are aggravated, sometimes with the addition of psychic automatism.

All of this confirms the complex pathogenesis of this disturbance, which has its outward clinical manifestation in the form of the "greater," nonuniform depressive-paranoid syndrome.

The complexity of the pathogenesis of the greater psychopathological syndromes is also confirmed by the characteristics of the depression that arises as a complication in chlorpromazine therapy.* The first characteristic of this depression is that it has been observed, as a rule, in the treatment of patients with the polymorphic (the greater) syndrome (that is, the hallucinatory-paranoid or depressive-paranoid type), but has not occurred in treatment of patients in a paranoial state or in cyclothymic depression (that is, those with the "lesser" or uniform syndrome).

Second, this type of depression occurred only when delusions and hallucinatory disorders and symptoms of psychic automatism had disappeared.

Third, its clinical manifestations were far from uniform. It was not simply a depression, but from its clinical manifestations it was a melancholia anesthetica, that is, a depression accompanied by dissociation from reality, depersonalization, excitation of thought and speech, akathisia, and disturbance related to sleep. In other words, it was not a simple syndrome, but a polymorphic syndrome like the previous one. The bioelectric mosaic corresponded to this description (FIGURE 13).

All these data permit us to regard this depression not as a complication, but as a phase of the complex pathogenesis of the disease, the treatment of which results in the neutralization of a series of pathogenetic links and thus changes the natural development of the process.

The orderly increase in complexity of the clinical picture of psychic illness as it progresses was first described by Magnan,[13] on the basis of his studies of chronic systematized hallucinatory-paranoid psychoses (the modern paranoid schizophrenia). However he tried to understand the genesis of this increasing complexity in psychological terms, in accordance with the traditions of Esquirol. For example, he treated the development of fantastic ideas of grandeur in patients with delusions of persecution as the understandable development of the personality: if the patient is being persecuted so relentlessly, this must mean that he is someone out of the ordinary.

This explanation, however, immediately becomes useless in an attempt to understand the genesis of various properties of delusions of grandeur and delusions of persecution. Delusions of persecution in these patients are logically consistent and interpretative, but the delusions of grandeur that

* Data of A. I. Smulevich, a co-worker in the clinic.[15]

develop are dreamlike and imaginal (eidetic): a type of unrestrained "fantasizi ing" aloud. Equally ineffectual is the psychological explanation of the transi tion, in the course of paranoid schizophrenia, from the paranoial state into th paranoid state, with the development of diverse symptoms of psychic automa tism (the Clérambault-Kandinsky syndrome).

FIGURE 13. Bioelectric mosaic of schizophrenic patient with symptoms of depressi resulting from chlorpromazine therapy.

At first glance, the psychological explanation of the origin of delusions guilt, judgment, and punishment from the depressive alteration of affect seem reasonable. However, how can we explain, in psychological terms, the disap pearance of these delusions despite the sharpest intensification of depressio which often occurs in chlorpromazine treatment of such patients?

It is impossible to explain the development of catatonic disorders arisi in the course of expansive paraphrenia, at the height of development of megal

maniac delusions of grandeur, either by psychologically understandable associations, by symbolism, or by psychological mechanisms of regression.

The stereotypic development and increasing complexity of psychopathological syndromes in the course of any psychic illness are amenable only to the causal type of analysis as an outward expression of pathophysiological mechanisms of higher nervous activity. The substitution and rise of complex syndromes as the psychosis progresses is the result of the automatic development of a functional disorder of the brain that grows and spreads among its structures.

Of the two main historical directions in which psychiatry has developed, as distinguished by Kurt Kolle[1]—the causal and the psychologically understandable—only the former is being carried to fruition by the science that is developing explosively in our own day. At present, psychiatry is still at the threshold of an understanding of the pathophysiological bases of the clinical manifestations of psychoses. These bases, naturally, are immeasurably more complex than they are represented here. In psychiatry, in contrast to somatic medicine, we still lack a composite theory of the general pathology of psychoses. It is true that the foundations of this theory have already been laid by the pathophysiology of higher nervous activity. Modern psychotropic agents are the instrument by which we can promote its further successful development.

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IMMUNOLOGICAL REACTIVITY IN SCHIZOPHRENIA AS INFLUENCED BY SOME MODERN DRUGS

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This report is an account of studies dealing with some peculiarities of immunological reactions in schizophrenia. These studies were carried out in the past five years at the psychiatric clinic of the Second Moscow Medical Institute by myself in collaboration with Y. A. Ilyinski and L. S. Koolikov (both of whom are psychiatrists) and in close cooperation with G. V. Vigodchikov and N. G. Olsoufiev, who are prominent Soviet specialists in immunology. These studies had a triple objective: (1) to clarify the influence of the nervous system on the immune process; (2) to investigate the mechanism of action of the so-called psychopharmaceuticals; and (3) to elucidate some problems in the pathogenesis of schizophrenia.

These investigations were carried out by using methods that enabled us to study immunobiological reactions kinetically at different stages of the active immunization process caused by inoculation of respective antigens. For this purpose two antigens were used: tularemia vaccine, to which the patients had never been exposed, and the staphylococcus anatoxin, one of the most common antigens. The immune reactions produced by these antigens are strictly specific, and the results obtained may be estimated numerically. These antigens never produce group reactions. Observations were made in 735 patients, most of whom had been treated for a long time in our hospital. Of these, 654 patients were schizophrenics; 58 oligophrenic patients and 23 patients with postencephalitic parkinsonism served as controls.

All patients were subdivided into two groups. The first group comprised patients who had never received active therapy; those under shock treatment or receiving chlorpromazine (aminazine) or reserpine medications formed the second group.

The indices of immunological reactivity obtained in schizophrenic patients were compared with those in (1) normal subjects, and (2) in patients with some other mental disease, who stayed in the hospital for about the same length of time and were under conditions similar to those of the schizophrenics.

The Role of the Nervous System in Immunity

From the biological standpoint the immunological mechanisms are components of homeostasis and of defense and adaptation reactions. As homeostasis is controlled by the nervous system, it may be postulated that immunogenesis is under the same control.

The role of the nervous system in the cellular aspects of immunity, particularly in phagocytic reactions, is clearer than is its relationship to the humoral forms of immunity.

It is well known that S. J. Metalnikov[1] was the first to report the possibility of reproducing cellular reactions of immunity and antibody response by conditioned reflexes. This first part of his statement was subsequently

confirmed by other investigators. However his later suggestion concerning the humoral factors was challenged in numerous experiments and was the subject of much discussion among Soviet immunologists.

The concept of the purely nervous mechanism of immunity has been supported by the collaborators of A. D. Speranskii,[2] D. F. Pletsityi,[3] O. Ostryi,[4] and others. The studies performed in the laboratories of P. F. Zdrodovskii,[5] A. D. Ado,[6] and others did not confirm either the hypothesis of antibody production by conditioned reflexes nor the assumption concerning the possibility of neural reception of antigenic stimuli and their transmission by nervous pathways. Under these conditions the studies of immunological reactivity in patients with defects of the central nervous system may be of certain interest.

The Investigation of Immunological Reactions in Schizophrenic Patients as Means to Study the Pathogenesis of Schizophrenia

In his work on the condition of the reticuloendothelial system in schizophrenia, F. Meyer[7] came to the conclusion that reduction of reactivity is typical of schizophrenia. Since then the problem of "the body reactivity" in schizophrenia has been given special attention in studies of the pathogenesis of this disease. Immunological reactivity is one of the forms of "the body reactivity."

In the Soviet literature of the postwar period many reports on the problem have been published. For the purpose of evaluation of reactivity most authors used such nonspecific indices as complement titers, phagocytosis index, and globulin fraction changes. It should be mentioned also that those investigators who applied immunological methods had different opinions on the pathogenesis of schizophrenia, as well as different aims and tasks.

With the aid of immunological methods some of them (G. Y. Malis[8]) tried to prove the virus etiology of schizophrenia. Others (A. S. Chistovich,[9] A. G. Shvedskaia[10]) suggested that pyogenic organisms played an important role in the etiology of schizophrenia.

According to most authors, however (V. A. Giliarovskii,[11] E. A. Popov,[12] A. V. Snezhnevsky,[13] A. D. Zourabashvili,[14] N. P. Tatarenko,[15] G. N. Plesso,[16] P. F. Malkin,[17] and others), neither the clinical course of the disease nor the results of laboratory and experimental studies prove the infectious origin of schizophrenia. These workers also regard the investigation of body reactivity by immunological methods as one of the many courses to pursue in studying the pathogenesis of schizophrenia.

Our present investigation is based on this concept.

Immune Reactions and the Mechanism of Psychopharmaceutical Action

This problem is being studied at present along the following lines: (1) clinical observations in patients during treatment; (2) neurophysiological analysis; and (3) neurochemical analysis. These lines of investigation may be supplemented with immunological studies.

In the course of clinical observation it was established that chlorpromazine is able to induce allergic reactions.

The substance acting as allergen is closely related with immunological reactivity. According to many authors, the action of reserpine is associated with

liberation of serotonin, which has the capacity to increase phagocytosis and th activity of mesenchymal cells: that is, it is related to the immunological re activity. There are some indications that narcosis and curative sleep in duced with the aid of drugs may influence the antibody production, ofte inhibiting it (P. F. Zdrodovskii).[18] According to our knowledge nothing ha yet been published on psychopharmaceutical action in immune reactions. I this report my colleagues and I present only those data that differ in variou groups of patients or in normal subjects.

Let us follow the course of immunological reactions in tularemia vaccination The vaccine was applied to the skin in the manner of small pox vaccine. I is harmless and induces only some hyperemia and skin infiltration around th scarifications. The immunological changes in vaccinated subjects can b estimated precisely by means of an agglutination test. The extent of ski reactions in our patients showed no marked difference from those in norma subjects receiving prophylactic tularemia vaccination. The differences i

TABLE 1

THE MEAN AGGLUTINATION TITERS IN SCHIZOPHRENIC PATIENTS AS COMPARED WITH NORMAL SUBJECTS

The predominant syndrome	Time after vaccination (days)				
	10	20	30	60	180
Paranoid	1:1	1:24	1:26	1:50	1:34
Apathetic imbecility	1:2	1:19	1:48	1:76	1:30
Catatonic agitation	1:1	1:12	1:38	1:40	1:30
Catatonic stupor	1:7	1:16	1:22	1:23	1:14
All schizophrenic patients	1:3	1:18	1:42	1:57	1:22
Normal subjects	1:4	1:16	1:59	1:83	1:63

the immune process were found only in limiting serum dilutions in agglutinatio tests. The kinetics of mean agglutination titers is presented in TABLE 1.

According to our findings, the immunological reactions in protracted case of schizophrenia with marked mental defects were somewhat low, compare to those in normal subjects. There is some indication of an association betwee the immunological reactivity and the clinical status of patients. Thus i catatonic stupor the antibody response was much lower than in normal subjects It was decreased, but not to such an extent, in the state of catatonic agitation In paranoid syndrome and in patients with apathetic imbecility, the antibod titers did not differ from those in normal subjects.

Thus the greatest change of immunological response toward reduction wa found in stuporous patients. The extinction of conditioned reflexes, as we as of many unconditioned reflexes, observed in these patients is indicative o the spread of inhibition into the brain stem. We may assume that the develop ment of immune response is considerably influenced by the subcortex.

To confirm this assumption a comparison of immune responses had to b made in patients with disorders of the cortex and in those with lesions an dysfunction of the brain stem and central grey matter formations.

For this purpose the oligophrenic patients in the state of idiocy and profound imbecility, as well as parkinsonian patients with a history of epidemic encephalitis, were vaccinated.

The results of agglutination tests are given in TABLE 2.

As may be seen, the immune response in oligophrenic patients was just as active as in normal subjects; in parkinsonian patients it was lower. The data obtained in this study confirm the assumption that subcortex dysfunction is more important than cortex dysfunction in the central regulation of immunity processes.

Six months after primary vaccination those patients whose condition did not change were revaccinated.

The differences in the new mean agglutination titers were not as marked as after the first vaccination. Therefore it may be stated that in revaccination the immune process is less dependent on the functional state of the central nervous system.

The study of staphylococcal immunity did not reveal anything new, compared to findings with tularemia immunity.

TABLE 2

THE MEAN AGGLUTINATION TITERS IN PATIENTS WITH SCHIZOPHRENIA, OLIGOPHRENIA, AND PARKINSONISM

Disease and syndrome	Time after immunization (days)				
	10	20	30	60	180
Schizophrenia	1:3	1:18	1:42	1:57	1:22
Oligophrenia	1:9	1:57	1:73	1:107	1:34
Parkinsonism	1:2	1:25	1:49	1:53	1:14

It is a well-known fact that as a result of close contacts with the facultatively pathogenic germs, specific antibodies may be found in blood even in the absence of clinical manifestations of disease. According to G. V. Vigodchikov,[19] the staphylococcus antitoxin content in normal serum does not exceed 0.25 antitoxin units (AU). In skin diseases it reaches 0.5 AU. In patients with suppurative surgical diseases it varies from 1 to 3 AU. The initial content of antitoxin in serum of all our patients was 4 to 6 times higher than normal.

This is probably due to the behavioral peculiarities of the mental patients.

Immunization consisted of four subcutaneous injections of staphylococcus anatoxin in increasing doses of 0.2, 0.4, and 0.6 ml. at 5-day intervals.

The fourth injection, 0.2 ml. of anatoxin (revaccination), was given 90 days after the first injection.

Serum antitoxin titers were measured before every injection and on the 20th, 50th, and 90th days after the first vaccination. The determination of antitoxin titers was also performed seven days after the revaccination. The results are summarized in TABLE 3.

As may be seen in the table, 10 days after the beginning of immunization staphylococcus antitoxin titers increased 4 to 6 times, compared with the initial values. The minimal rise was observed in catatonic stupor cases.

Three months later the antitoxin titers had declined considerably. Aga the lowest titers were recorded in stuporous catatonia.

The fourth anatoxin injection had caused an increase of antitoxin titer which again were least in patients with catatonic stupor. In the initial stag of immunogenesis, the greatest antitoxin titers were found in the serum parkinsonian patients, but later there was a rise in titers in these cases in spi of repeated injections of the antigen.

These facts may be interpreted as inhibition of immune reactions in parki sonism. The antibodies we studied were of a different nature. The tularemi agglutinins are chiefly α-globulins. The staphylococcus antitoxin (G. V. V godchikov[19]) is associated primarily with β- and γ-globulins. On the basis these considerations, we may state that our studies have revealed close correl tion with, or almost coincidental to, the immune reactions caused by differe antigens in similar groups of patients.

The differences in immune response depended more on the clinical status our patients than on the nature of the antigens used. This indicates th

TABLE 3

THE STAPHYLOCOCCUS ANTITOXIN CONTENT IN THE SERUM OF SCHIZOPHRENICS AND PATIENTS WITH OLIGOPHRENIA AND PARKINSONISM

Disease and syndrome	Day of the first injection	Time after vaccination (days)				
		5	10	20	90	97
All cases of schizophrenia	1.6	5.0	8.4	6.3	6.2	8.3
Catatonic stupor	1.7	4.0	6.4	6.6	4.2	5.0
Parkinsonism	2.2	6.0	9.6	7.2	6.2	6.2
Oligophrenia	2.3	5.6	8.8	6.4	6.4	8.4

dependence of the immune response on the central nervous system's function condition. Let us proceed to data obtained in studies of immunological rea tivity in connection with modern treatment of schizophrenia. Observatio were made in schizophrenic patients who had received insulin (hypoglycemi and shock doses), chlorpromazine (aminazine), and reserpine.

Chlorpromazine was given I.M. in doses of 150 to 400 mg. per day. Rese pine was given in doses of 7 to 12 mg. per day. The insulin shock therap course consisted of 20 to 35 shocks induced every day except Sunday. Th shock doses of insulin in different patients varied greatly. The results of ou observations are presented in TABLE 4; the results of staphylococcus vaccin tion are given in TABLE 5.

These statistically significant figures reveal that only insulin shock therap has stimulated the immune response in schizophrenic patients. All the oth methods of treatment did not affect it substantially.

In contrast to the results observed in schizophrenic patients vaccinate with tularemic antigen, it was found that after staphylococcus antigen inje tions, aminazine stimulated the antibody response to the same degree as insuli

However, this effect has been detected only at about 20 days after the in

munization. It should be noted that immunization and aminazine therapy were started simultaneously.

It should be considered that the tranquillizing stage induced by aminazine (which is preceded by the somnolent stage) begins 8 to 12 days after the administration of the drug, and it is exactly at this time that the capacity of aminazine to enhance immunogenesis becomes evident. In his inaugural speech at the Paris Colloquium on chlorpromazine, Jean Delay[20] opposed the neuroleptic action to that of the shock.

Table 4

The Mean Tularemia Agglutinin Titers in Schizophrenic Patients Subjected to Different Methods of Treatment

Methods of treatment	Time after vaccination (days)			
	10	20	30	60
Initial period of insulin treatment	1:2	1:7	1:20	1:50
Insulin treatment during periods of shock	1:4	1:32	1:78	1:109
Aminazine (chlorpromazine)	1:3	1:26	1:35	1:61
Reserpine	1:1	1:25	1:65	1:53
Patients not subjected to therapy	1:3	1:18	1:42	1:57

Table 5

The Staphylococcus Antitoxin Titers of Schizophrenic Patients Treated with Insulin and Chlorpromazine (Aminazine)

Methods of treatment	Period of observation (days)						
	Day of the first injection	5	10	20	50	90	97
Insulin therapy (hypoglycemic and shock doses)	1.4	2.7	7.5	13.5	10.6	8.0	9.8
Aminazine	1.2	3.5	8.7	14.7	16.5	14.5	18.0
Patients not subjected to any therapy	1.6	5.0	8.4	6.3	—	6.2	8.3

The state of neurolepsia is characterized by complete rest of the body. On the contrary, in the state of shock an anxiety effect is produced.

In spite of the differences between the effects of insulin shock treatment and chlorpromazine therapy on the nervous system, both are able to enhance immune response, although this effect appears at different periods of time and is induced through different immunogenic systems.

The chief objective of our studies was the accumulation of accurate facts.

The time for broad generalizations has not yet come. Taking into consideration the opinion of prominent Soviet immunologists (A. D. Ado,[6] P. F. Zdrodovskii,[18] L. A. Zilber[21]) that the central nervous regulation of immune response

is effected through the hypothalamus-hypophysis-adrenal system, we mus point out that our studies revealed a rather labile connection between the statu of the central nervous system in our patients and the immune response. Th connection is partial and indirect. It is a correlation rather than a functiona association.

We must state in conclusion that our observations do not quite coincide wit the opinion that reactivity is decreased in schizophrenia. Immune respons is certainly decreased in certain forms of schizophrenia and some other menta diseases, but it may be stable or even increased in others. These correlation are especially complicated during insulin shock treatment and neurolepti therapy. Nevertheless there is some tendency toward the immune respons activation as a result of both methods of treatment.

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STUDIES TOWARDS CORRELATING BEHAVIOR WITH BRAIN ACTIVITY

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It was a most rewarding experience for me—and I am sure for everyone i terested in the learning process and behavior and, particularly, the attempt correlate these with activity of the nervous system—to review the presentati by Kupalov.

I was most interested in Kupalov's introductory remarks. He cautioned against making too many sweeping hypotheses concerning behavior on th basis of physiological data alone. His illustration to the effect that a hyp thetically perfect physiological set-up with recordings from virtually eve cell of the brain, while providing a tremendous quantity of physiological dat would give no information concerning behavior, is excellent. He presen a viewpoint with which I heartily agree.

With the techniques of the basic sciences—physiology, anatomy, chemistr and others—we can investigate the brain. These techniques, however, do n and never will provide direct information concerning behavior. In order investigate behavior, we must employ other techniques: the techniques of th behavioral sciences. With animal experimentation, the conditioned refle methods have proved most useful.

Research studies in my department at Tulane are in the same area as tho presented by Kupalov. I therefore can best discuss his presentation by me tioning some of the concepts and some of the data my co-workers and I hav obtained.

I am by trade a psychiatrist and neurologist and, therefore, primarily inte ested in human behavior. In our research studies at Tulane, efforts have bee directed toward correlating data obtained through employment of the tec niques of the basic sciences with data obtained through psychological method We have attempted to cross-interpret the inspective data of physiology, ana omy, and chemistry with the introspective data obtained through reports b the patient of his thoughts, feelings, and emotions. Many investigators com plain that utilization of introspective data, or data from the reports of th patient, is so complicated as to be impractical and scientifically unsoun Admittedly, the handling of these data is difficult. On the other hand, it is method that, by far, provides us with the most material. Failure to use th methods of introspection would deny us the largest potential source of dat on human behavior. In our studies directed towards integrating human b havior with activity of the central nervous system, we direct our attentio toward attempting to make cross-interpretations between these two areas study. We recognize that there never can be a one-to-one relationship betwee nervous system activity and behavior. For our studies employing the inspe tive methods of the basic sciences, as well as the introspective methods psychiatry (directed toward the intense investigation of the individual), w use extensively the theoretical framework of modern psychiatry: psychod namics. We consider it of importance to emphasize that psychodynamic theo

is, in its basic principles, very similar to the theoretical concepts of Pavlov. Perhaps I can best illustrate this by reviewing briefly the highlights of the dynamic theories of behavior.

We consider the behavior of an individual to be an ongoing interrelationship between the basic biological needs, often referred to as instincts or drives, and the learning process. The basic moving force is the biological need, and the behavioral pattern the individual employs to satiate the need is determined by learning. This can be illustrated with the following formula:

		(Biological)		(Learning)		
Equilibrium_1	→	Need	→	Activity	→	Equilibrium_2
		(Tension, pain)		(Pleasurable)		

The individual thus moves from one equilibrium to another. He enters into a state of disequilibrium when needs develop that are associated with tension or discomfort. The needs are basically related to survival (of individual or species). The activity to remove the state of tension, that is, the manner in which the individual satisfies his basic biological urges or drives, is dependent upon his conditioning. The pleasure experienced through activity is usually proportionate to the intensity of the need. For example, eating of food is very pleasurable if one is very hungry, whereas immediately following a satisfying meal, the ingestion of even the most delicious meal is not pleasurable. The activity results in the establishment of a new equilibrium that prevails until new needs related to the ongoing biological process develop and thus reactivate the cycle. This simple, very basic formula accounts for the basic movements or dynamics of behavior. Aside from such simple reflex behavior as is associated with startle, all human behavior fits into this formula. In this framework, the pattern the individual employs to dispel the need is determined by the learning process. Each of us meets situations in the "here and now" and anticipates the future in terms of our past learning experiences.

Modern psychodynamic theory considers not only adaptive or normal behavior, but also maladaptive or abnormal behavior within this framework. The key factor in neurotic behavior is inappropriate fear. The behavioral patterns described under a variety of headings represent ineffective attempts to relieve the intolerable or inappropriate anxiety. Anxiety occurs as a consequence of faulty learning, and can occur in any given area of behavior. For example, the child is threatened in regard to sexual behavior and is taught that it is something for which he will be punished. He thus develops inappropriate anxiety when he attempts to satiate the need. If, as a result of his faulty learning, he develops excessive fears of authoritative figures, he then will have a neurosis with symptoms centered about disciplinary activity. The principal point is that the inappropriate anxiety evolves from faulty learning experiences in which the individual is taught to fear something that, in the interest of adequately meeting life situations, he should not fear. This same basic idea could be expressed equally well using Pavlovian terminology, by stating that faulty conditioning patterns have been set up in regard to one or more areas of behavior out of which behavioral patterns develop that are referred to as neuroses. These neurotic symptoms, figuratively speaking, constitute a type of repair. Al-

though they handicap the individual in his performance, they serve to lessen inappropriate anxiety.

In the Tulane studies, designed to correlate brain activity with behavior, we have carried out many varied experiments and have developed a number of new techniques for studying the nervous system. Early in our studies we developed a hypothesis that served as a foundation for evolving new methods of study (TABLE 1). This chart is a crude schematic attempt to make some gross cross-correlations between the psychodynamic or psychological levels and the neural levels within the nervous system. Needless to say, we do not consider that there are concrete levels such as this chart would tend to indicate; those familiar with activity of the nervous system realize that the brain functions as an integrated whole. This chart, however, has a useful purpose in attempting to devise ways of exploring the manner in which this whole system is integrated. The data forthcoming from the Columbia Greystone Project significantly contributed to this formulation. In that study, selected areas of the frontal lobes of a group of chronic psychotic human subjects were removed. The most pertinent finding was that removal of parts of the cortex resulted in a lessening of emotion associated with past learning experiences. There was a reduction in the painful affect associated with faulty learning. Patients handicapped because they adapted to the "here and now" and anticipated the future in terms of inappropriate anxiety of emergency were improved, although there was an impairment in their ability to plan in the future. This change, however, was to their advantage, because it enabled them to live in terms of the present. Another key observation was that the basic machinery for the expresion of emotion and feeling remained intact. Many of the patients in the study were severely schizophrenic with a lack of affect and feeling; the frontal lobe operation did not alter this characteristic. Kupalov mentioned in his paper that the process of irradiation requires an intact cortex. The results we obtained with removal of parts of the frontal lobe in these disturbed patients indicate that the process of pathological radiation was lessened, thus supporting Kupalov's contention.

During and immediately following the Columbia-Greystone Project, my attention, partly because of the observed results with the patients, was directed to the study of the cortical-subcortical interrelationships. Inasmuch as the removal of cortex resulted in lessening of painful emotion associated with memory experiences but did not alter the machinery for expression of emotion, we hypothesized that these frontal lobe areas played into structures lower in the nervous system: structures not related to feeling and emotion. Many experiments were conducted with animals. My attention was directed first to the neostriatum through the work of the Mettlers,[2] who reported that damage to these structures resulted in a severe defect of emotional expression. Our studies suggested that the septal region was more implicated in this phenomenon. I shall describe briefly the series of studies resulting from the observations.

Septal ablation resulted in flat, affectless animals. This behavior frequently was associated with disturbances in electrolyte balance and sugar metabolism.

In acute experiments in which background motor activity first was induced

TABLE 1

LEVELS OF BEHAVIOR*

Relation of organism-environment	Level				
	Neural.	Psychodynamic	Regulatory signal behavior recording and anticipating benefit	Regulatory signal recording and anticipating damage	Behavior
Intellectual cultural circuit	Cortical	Thought	Secure utility and pleasure avoid damage		
Sensory-nervous motor circuit	Sept.-hippo.-amyg. distance receptors	Emotional	Love → Hold-possess Catch-ingest Hope → Sustaining	Rage → Fear →	Combat Escape
Metabolic circuit	Reflex contact receptors	Hedonic (sentient)	Pleasure → Absorption	Pain → Loss of pleasure →	Riddance Retrieval

* Adapted from unpublished data compiled by Sandor Rado.

it was found that stimulation to the septal region resulted in facilitation of thi induced background motor activity, suggesting a cortical facilitation.[3,4] I contrast, stimulation more caudal, that is, caudal to the anterior commissure while facilitating the neurone arc, did not specifically facilitate induced back ground activity.

Stimulation of the septal region in animals with chronically implante electrodes produced alerting with desynchronization of the electrical recording The animals appeared to enjoy the stimulus; they ate heartily, for exampl This response was quite different from that obtained with stimulation of th more caudal structures, including the tegmentum of the mesencephalon When stimulation was applied behind the anterior commissure and back int

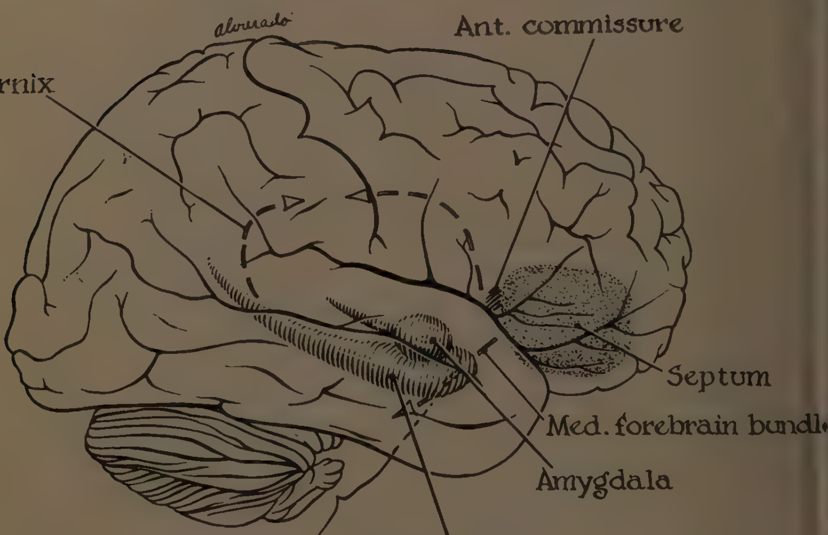

FIGURE 1.

the mesencephalon, the animals developed a diffuse restlessness, in contrast t the seemingly enjoyable response to stimulation of the septal region.

We concluded that the septal region produced diffuse activation of th entire brain. Therefore we referred to this region as the facilitatory center an important part of the facilitatory circuit.

The septal region is part of the rhinencephalic brain. Its connections hav been described by numerous authors[5,6,7] in addition to ourselves.[8] FIGURES 1 and 2 show the location of our septal region and some of the more prominent anatomical connections.

These were our principal background findings at the time we elected to carry our studies to human subjects, from whom we were able to obtain more signifi cant data with which to make cross-correlations between the brain and be havior, since humans were able to talk to us and tell us their thoughts, feelings

and emotions. We were also able to correlate the reports of the patients with their physiological data. We initiated our work with human subjects late in the fall of 1950, employing depth-electrode techniques for study of the brain. FIGURE 3 is a photograph of the stereotaxic instrument for humans designed and built in our laboratories at Tulane. Our technique for implanting depth electrodes gradually has been improved, but has not been modified markedly since 1953.[9,10] The photograph shows the bone button that fits the trephine hole to fix the electrodes in position. The electrodes, after being fixed at the

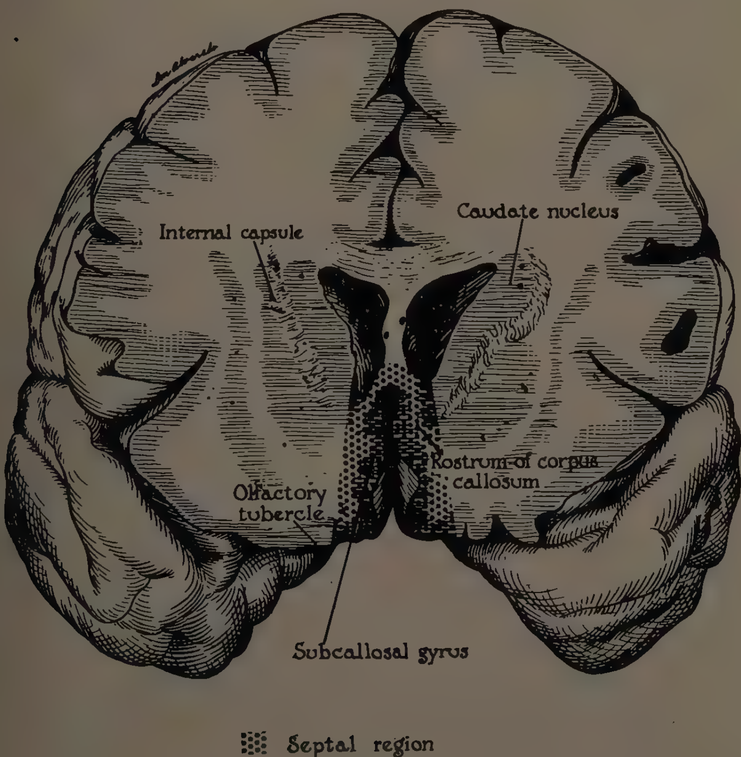

FIGURE 2.

trephine hole, are brought posteriorly under the scalp for 6 to 8 inches before their exit from the skin. This method completely eliminates pathways for the spread of infection. With this technique we can hit within 1 mm. of the target area anywhere in the brain and, by thus fixing the electrodes, can keep them implanted in the same regions for periods up to two years. The electrodes are soldered to special plugs that the patient can cover with a cap. It is simple to plug into the electrodes for recording or electrical stimulation, and we thus are able to study brain activity at regular intervals. We have followed patients with a variety of disorders, including psychosis, epilepsy, and intractable pain without primary involvement of the nervous system. It has been possible to

FIGURE 3.

study the patients while they are exhibiting a wide variety of behavioral patterns.

FIGURE 4 is an X ray of a patient with electrodes in position in the caudate, septal region, hypothalamus, tegmentum, and hippocampus. Other patients have had many more electrodes implanted: up to a total of 39. With this technique we have been able to make significant correlations between brain activity and behavior: correlations in association with emotion and feeling. These behavioral expressions always have been correlated with activity in the septal-hippocampal regions, that is, parts of the olfactory system. FIGURE 5, an electroencephalographic recording, illustrates this phenomenon. When the patient was severely frightened as a result of recalling painful past memories, spindling appeared on the records from the hippocampus and sometimes from the septal region. At the point indicated by the arrow, the patient was given a sample mathematical problem that distracted him from his emotional thinking and the high-amplitude spindling, focal in the hippocampus, disappeared. Later, he again was asked to tell of the emotionally charged memories and the spindling returned. We have observed this same phenomenon in a large series of patients.

Henry Lesse, who worked in the laboratories at Tulane when these observations were made on patients, conducted a study with cats in order to explore this phenomenon further. The cats were conditioned with an adverse response and, when fearful, they displayed this same type of spindling.[11]

Much has been written concerning the tegmentum of the mesencephalon, and much has been conjectured concerning that region of the brain and behavior. We have implanted electrodes into the caudal diencephalon and the rostral mesencephalon tegmentum in 6 of our series of 48 patients, and in no instance have we been able to show a correlation between the recordings from that region and the behavioral state of the patient.

The spindling activity we observed in the recordings from the hippocampus, amygdala and, occasionally, from the septal region, appears when the patient is in an intense emotional state, whether this emotion is painful, that is, when it is fear-rage, or is pleasurable; for example, when it involves love and pleasant anticipation.

In addition to this striking correlation between brain activity and the expression of emotion, we also were able to make consistent correlations between psychotic behavior and the brain recordings. The majority of the patients in our series have been chronic schizophrenics. Our initial therapeutic rationale for carrying these studies to humans was based on the idea that stimulation to the septal region might be a useful treatment for the severely ill schizophrenic patient. The schizophrenic patient displays a severe disturbance in his affect. He is flat, out of contact, and generally reduced in his level of psychological awareness. We have been impressed with the observation that schizophrenic patients have a disturbance in their pleasure feelings, that is, in their ability to feel pleasure. Our clinical observations have led us to postulate that the most consistent lifelong basic defect in the schizophrenic is his inability to integrate and feel pleasure. All other symptoms, well catalogued by numerous authors, seemingly are secondary to this. Animal studies have shown that ablation of the septal region causes the animal to develop a disturbance in

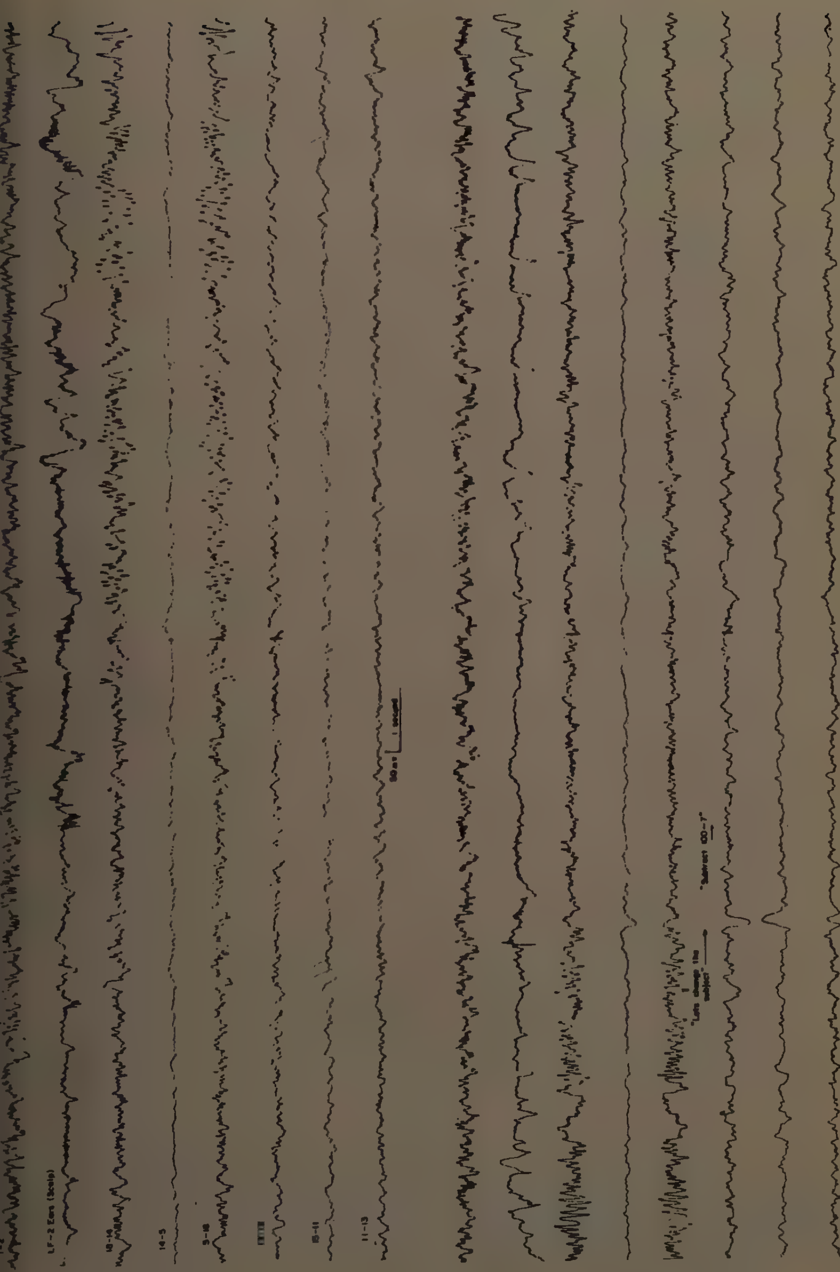

FIGURE 5.

affectivity. The animal is flat and out of contact, often with catatonic behavior. With stimulation to the septal region, the animal is alert, in much better contact with his environment and, seemingly, has a pleasure response to the stimulation. Physiological studies showed that the stimulation activated the brain. Recording data we obtained from human subjects supported our hypothesis that, possibly, this region was functioning abnormally in the psychotic schizophrenic patients.

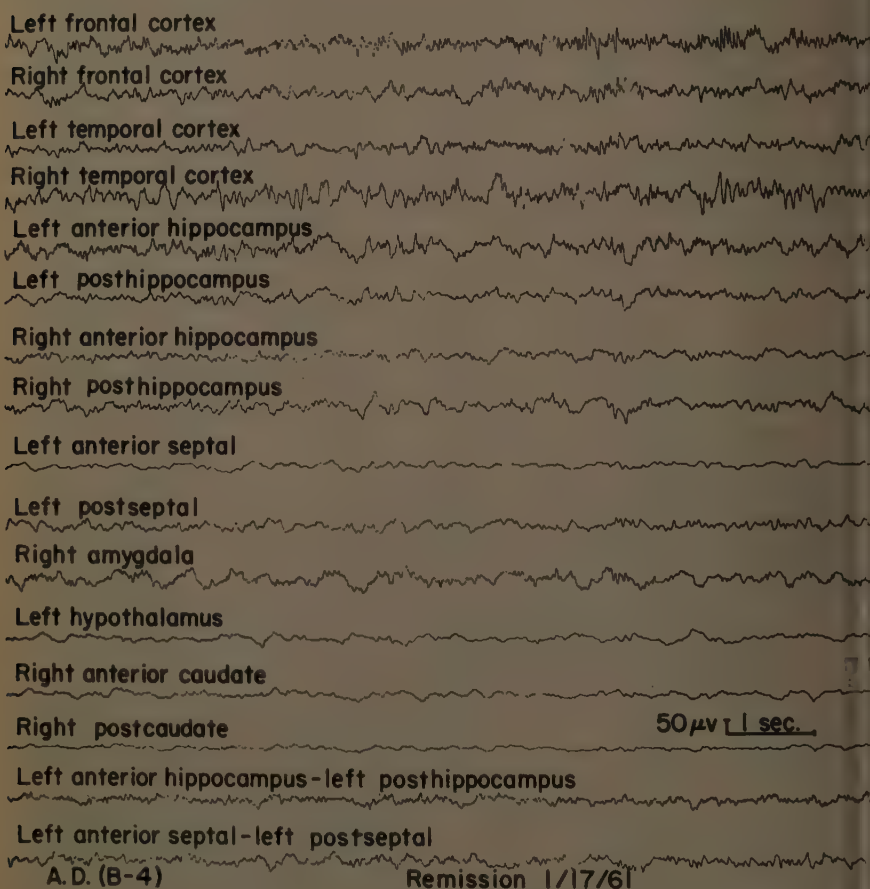

FIGURE 6.

FIGURES 6 and 7 are recordings from a schizophrenic patient during a period of remission and during a period when he was actively psychotic. The first recording approaches the type that we have seen in our nonpsychotic control subjects. However, when the patient is severely agitated, marked changes in the recordings from the amygdala, septal region, and hippocampus appear in association with his clinical state. The recordings from the cortical leads did not reflect these changes, nor do the recordings from other deep regions of the brain.

We have stimulated a large number of subcortical regions of the brain. When we stimulated the septal region of conscious human subjects, they usually reported that "it felt good," essentially a pleasure response. The patients became alert and performed psychomotor tests more efficiently. In our experience, the septal region is the only region that, when stimulated, results in a pleasure response. All other regions, including numerous areas in the hypo-

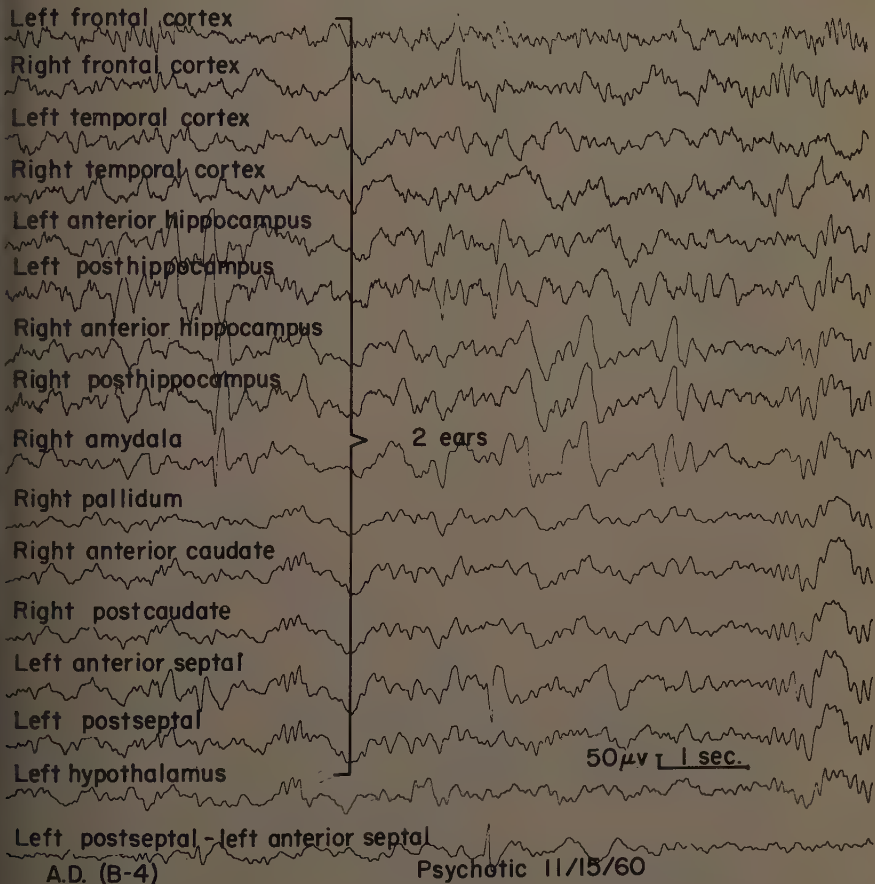

FIGURE 7.

thalamus, tegmentum of the mesencephalon, hippocampus, and amygdala, resulted in varying degrees of discomfort when stimulated; the most marked discomfort resulting with stimulation of the mesencephalon. Stimulation of the caudate nucleus and putamen had little effect, although, on occasion, patients became drowsy.

A few investigators in other centers have employed depth-electrode techniques. In no instance, however, have the electrodes been implanted with the same precision nor for a period of time comparable to the two-year period of

our studies. Thus other investigators have not accumulated data comparable to the data from the Tulane studies.

After demonstrating a consistent correlation between altered brain physiology and the psychological state, we began to investigate the nature of the basic process that created those alterations in brain function that were basic to the psychotic behavior. A number of studies were conducted, culminating in the isolation of a fraction from the serum of schizophrenic patients that we named taraxein. FIGURE 8 is a chromatogram from a DEAE cellulose column. When

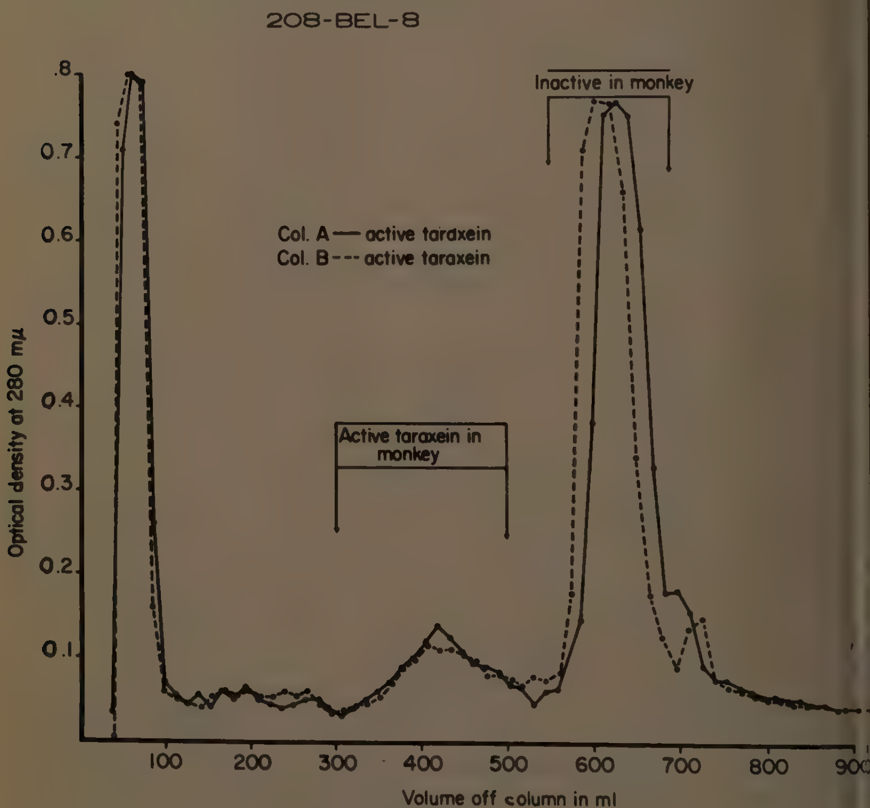

FIGURE 8.

the taraxein fraction was injected into monkeys, it produced changes in the recordings similar to those we had obtained from psychotic schizophrenic patients. In association with this, the monkeys became dazed and catatonic. M. P. Bishop, of the Tulane group, has reported that rats injected with schizophrenic plasma show significant impairment of learning as compared with animals injected with normal plasma or saline[12] (FIGURE 9).

In order to explore more completely the nature of the changes that take place in the brain, we have evolved a precision biopsy technique,[13] making it possible to conduct biochemical studies on tissues from specific, predetermined brain regions.

It would seem that at this stage of marital harmony between Pavlov and Magoun, we might try a triangular arrangement, with biochemistry acting as the paramour.

With the stereotaxic-biopsy technique, the VIM Universal Silverman biopsy needle was modified for cutting out the tissue. The needle is positioned in the brain, using coordinates determined from X-ray pictures taken with the cassettes mounted on the stereotaxic apparatus. Biopsies were obtained within 1 min. after removal began and thus were suitable for fixation with osmic acid and study under the electron microscope. FIGURE 10 is an electron microscopic visualization (×20,000) of a biopsy from the septal region of an epileptic

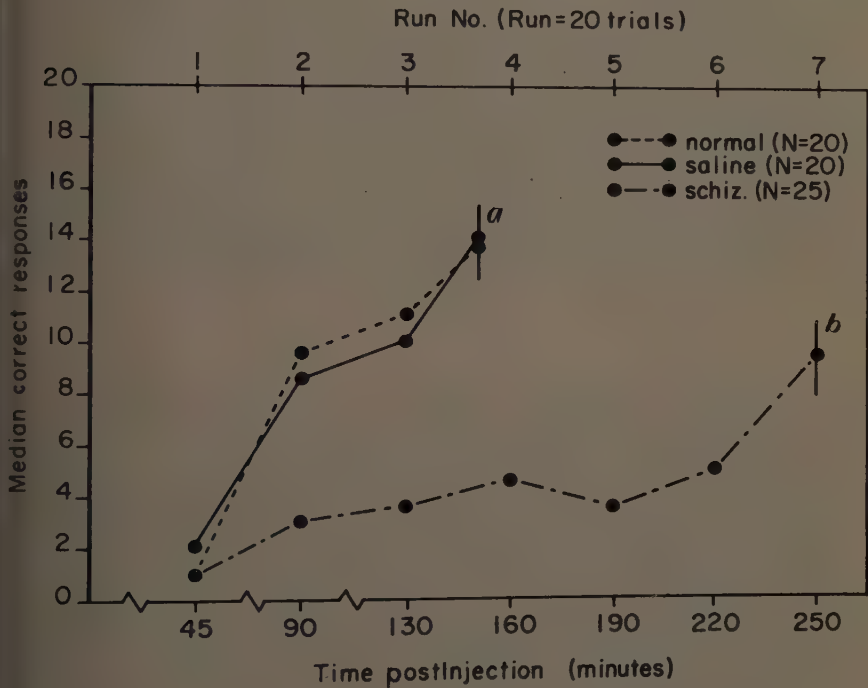

FIGURE 9.

patient. Other procedures employed in studying the tissues included histochemical staining, study of enzymic activity against several substrates, histological examination, and growth of tissue cultures. Our purpose was to investigate the nature of the intracellular process responsible for the physiological changes. FIGURE 11 shows the site of biopsy removal from the caudate nucleus of a rhesus monkey. The biopsy was taken 15 min. following an injection of taraxein while the monkey was displaying maximal symptoms from the substance.

It is our concept that these methods of study will give additional information concerning the nature of altered brain function in conjunction with a variety of diseases and thus enable us to make more effective cross-correlations between the brain and behavior.

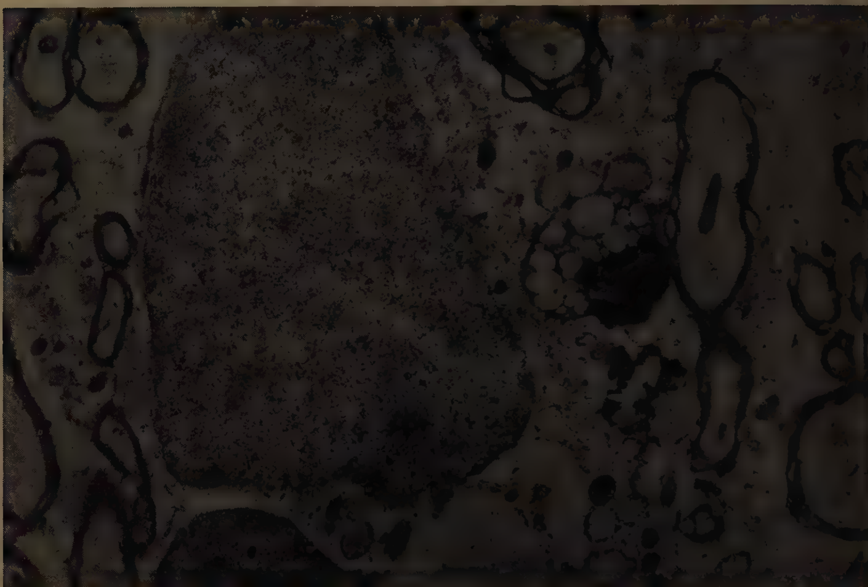

FIGURE 10.

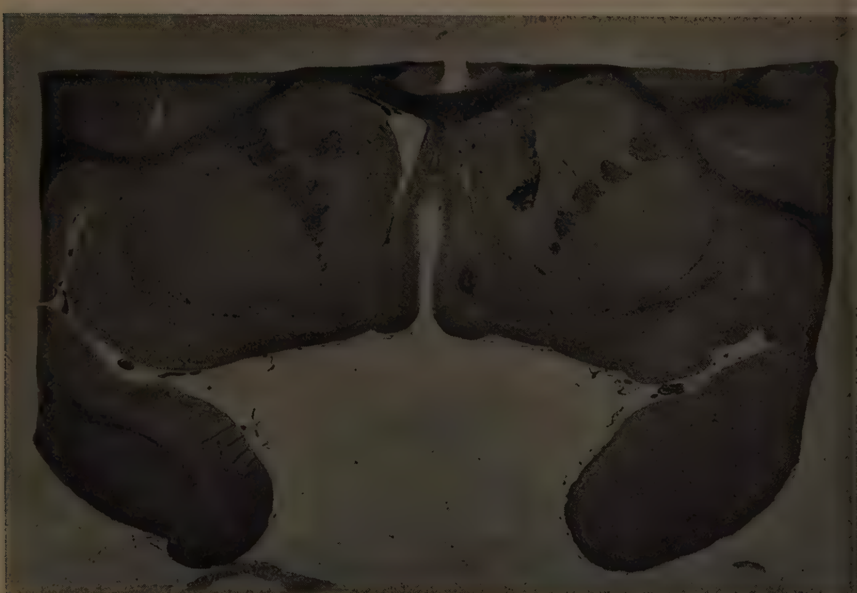

FIGURE 11.

In conclusion I congratulate Kupalov on his most interesting presentation. I have gained some valuable suggestions from reading his paper.

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DISCUSSION: PART V

Heinz E. Lehmann (*Verdun Protestant Hospital, Verdun, Que., Canada*) When one is called upon to discuss a paper by another scientist, there presents itself at once the need to find an opening that sounds appropriately complimentary, preserves a decent modicum of sincerity and, of course, leaves a nice opening for the blistering attack that is to follow. However, when one is called upon to discuss a paper presented by a foreign colleague from a far-away country the need to find that opening may grow into a rather embarrassing problem.

Once I had read A. V. Snezhnevsky's paper I knew that I had been spared this embarrassment. The research data he reports are highly original and left me in that state of delightful excitement that comes when one has learned something genuinely new and unexpected. The thoughtful and tolerant manner in which Snezhnevsky introduces and concludes his presentation made it very clear that he would not take it amiss if I did not agree with every point he made. Moreover, fortunately, he has made enough points with which I do not entirely agree to make this discussion a challenging and stimulating task.

There are three different aspects of Snezhnevsky's paper, and each of them must be dealt with in its own right. First and most important, there is, the original research and the objective data it yielded. Second, there is the psychopathological school to which Snezhnevsky belongs, the particular ways in which he sees the natural history of mental disease unfold, and the particular ways in which he groups and diagnoses his patients. Third, there is the great and controversial theory, developed by Pavlov, that provides Snezhnevsky with the concepts and mechanisms that allow him to explain the different behavioral phenomena he observed in relation to each other.

In his introduction, Snezhnevsky distinguishes the three basic approaches to modern psychiatry: the psychological, the clinical, and the physiological. He points out—and here I wholeheartedly agree with him—that no single approach contains the "royal road" to psychiatry: all approaches are still in the early stages of their development. Only a well-tempered comprehensive study of psychiatry, using the method of multifactorial analysis, will allow us to come to grips with the reality of the situation and to make progress in our search for understanding and explanation of behavioral phenomena.

Having stated his intention to use psychopharmacological experiments as tools for the investigation of the pathophysiology of higher nervous activity, Snezhnevsky then goes on to report the results of his research with the toposcope. This very remarkable instrument, which one may term a super-encephalograph, has been in existence for some time but, to my knowledge it has thus far served only to a limited extent for neurophysiological studies; its particular suitability for the study of complex psychiatric disturbances has not been exploited in the past. Through a network of 50 electrodes this instrument covers, like an umbrella, the electric activity of the cerebral cortex over its entire surface by recording all 50 potentials simultaneously. Furthermore, these 50 potentials are displayed in a manner that is familiar to and favored by the psychiatrist, namely, as a configuration rather than as a number of

disparate magnitudes, which would be the image from the type of recording that is more familiar to the neurophysiologist. The dynamic changes taking place in these recordings are perceived as modifications of a multifactorial *Gestalt* in spatial extension, instead of as a number of singly presented factor changes over a period of time.

If you will permit a digression for a moment, it is as though the mode of conceptualization for the psychiatrist finds its analogue in the visual modality of perception, in which interrelations of many different factors are established simultaneously in the dimension of space, while the mode of conceptualization for the neurophysiologist would be reflected in the auditory modality, in which interrelations of different factors are established in sequence, in the dimension of time.

I am trying—perhaps not quite as subtly as I had hoped—to build a case for the differentiation of the psychiatric from the neurophysiological approach, a differentiation to which Snezhnevsky probably would not subscribe. However, I shall come back to this point later.

The output of the toposcope is the bioelectric mosaic, and it is here that our Soviet colleague has made his important discoveries. Snezhnevsky has shown us that this bioelectric mosaic has the following characteristics in the paranoid schizophrenic:

(1) The dynamic quality of the mosaic is greatly reduced; that is, few spontaneous changes of the electrical configuration are observed in contrast to the normal mosaic, which is in constant movement.

(2) The schizophrenic mosaic is much less responsive to external influences, such as light stimuli or pharmacological excitants, than is the normal mosaic.

(3) The schizophrenic mosaic, particularly in the more chronic stages of the illness, frequently displays inert foci of hyperactivity upon the application of light or drug stimuli, but also sometimes independently of such stimulation.

(4) The schizophrenic mosaic not infrequently is asymmetrical in appearance.

(5) The schizophrenic mosaic is often characterized by general hypoactivity.

The characteristic feature of the mosaic during a cyclothymic depression is the very marked reduction of all electrical activity, and the mosaic shows changes toward normal activity when pharmacotherapy with a monoamine oxidase inhibitor is instituted and the patient's clinical condition improves. Such reversal of the disturbed bioelectric pattern toward the normal under drug therapy has also been noted by Snezhnevsky when schizophrenic patients improved with phenothiazine treatment.

A few of these observations had been made previously in what might be described as piecemeal fashion by ordinary electroencephalography. For instance, the asymmetry of cortical electrical activity is almost diagnostic of schizophrenia when it is observed in a patient without neurological abnormality. However the instantaneous availability of a configuration of different features makes the toposcopic method a very desirable diagnostic tool. Its value is further enhanced by the apparent possibility of following the clinical course of a mental disease through toposcopic analysis, even during stages of clinical remission when no overt symptoms are present. The toposcope might then actually do what we had hoped conventional electroencephalography would do when it was first introduced: namely, provide us with objective criteria for

psychiatric diagnoses and, in addition, allow us to obtain insight into pathological conditions and processes that could not be perceived in any other way. Until now electroencephalography has been rather frustrating to the psychiatrist, and only quite recently has new hope appeared on the research horizon with the introduction of electronic frequency and pattern analysis and with the promising experiments on evoked potentials. It might well be that the toposcopic method is the real answer to the problem and that Snezhnevsky has stolen a march on the other electroencephalographers in coming to the aid of psychiatrists.

The incorrigible clinician in me invariably raises a small but persistent voice leading me to say now that I wonder whether it would be possible to apply the toposcopic method to many psychiatric patients. Many acutely or chronically disturbed patients are not even cooperative enough to take an ordinary electroencephalogram, much less to tolerate the attachment of 50 different electrodes. I ask Snezhnevsky whether, in his opinion, the method could still serve a diagnostic purpose if the patients were pharmacologically tranquilized while undergoing the procedure, or whether the introduction of the pharmacological agent would obscure the diagnostic picture to a degree at which it would no longer be reliable. If it were possible to quiet a disturbed patient with, for instance, chlorpromazine, and still obtain an objective diagnosis, I, for one, and many another psychiatrist would soon start searching for funds to have one of these machines made.

I should like to obtain some information on the cost of such a toposcope. I am not only thinking of the original purchase price, but rather of the problem of maintaining and running an instrument of such high complexity. To calibrate all channels and reduce artifacts to a minimum must call for a very expert technician indeed.

Perhaps, however, the toposcope is primarily a research instrument, and my overly zealous clinical attitude has made me jump to premature conclusions with regard to its practical applicability as a diagnostic tool. I should like to know Snezhnevsky's views on this question.

As a research instrument the toposcope seems to offer many intriguing possibilities. If we use it as a research instrument rather than as a clinical tool, we place the emphasis on the general laws and mechanisms that we might discover through its use: we consider the individual patient as a paradigm from which we abstract, instead of considering him as a empirical subject in his own right. Snezhnevsky's principal purpose seems to have been to make his experimental findings the basis of a theoretical explanation of the pathological processes underlying paranoid schizophrenia.

At this juncture I shall refer to some of the issues on which Snezhnevsky and I are not in perfect agreement: the questions of experimental methodology, of diagnostic terminology, of psychopathological conceptualization, and of pathographic description of the course of a mental disease. Snezhnevsky bases his clinical thinking and his theoretical deductions on what he calls the developmental stereotype of paranoid schizophrenia. This developmental stereotype, according to him and the psychopathological school to which he belongs, manifests itself in four distinct stages he calls the paranoial, the paranoid, the paraphrenic and, finally, the stage of secondary catatonia. These

four stages are distinguished primarily by the increasing organization and rigidity of their psychotic symptomatology, which is in this case chiefly expressed in the form of delusions.

Snezhnevsky refers to this progression of symptoms that would be acknowledged, of course, in many cases of paranoid schizophrenia by most clinical psychiatrists anywhere in the world, as a developmental stereotype. That would imply that there can be few if any exceptions to the rule of such a sequence of stages. Nevertheless Snezhnevsky says: "To be sure, the course of paranoid schizophrenia very often deviates considerably from that described . . . but the electroencephalographic investigation . . . was carried out on patients in whom the disease had followed the classic course." If the course of the disease deviates considerably very often, one can hardly speak of a stereotype.

Furthermore, how are we to interpret the remark that the cases for the electroencephalographic investigation were chosen only from among the typical representatives of the "stereotype?" In the terminology of experimental design that is today so dear to the heart of every United States researcher, Snezhnevsky selected his experimental sample with an explicitly stated bias. Such a procedure is, of course, quite legitimate as long as the experimenter draws his conclusions only in respect to the sample he examined. Snezhnevsky, however, extrapolates his findings to the objectively undefined sample of *all* paranoid schizophrenics. Or did I misunderstand him?

His electrophysiological discoveries are of considerable and original value for the sample he examined, and they throw new light on some of the basic mechanisms underlying the pathology in these cases. Such experimental findings would justify making certain more or less speculative assumptions on physiopathological processes in other mentally sick patients or in schizophrenia in general. Such assumptions would then be hypothetical inferences based on certain experimental findings that the investigator believes to be representative of others, but one could not thus claim to have established experimental proof of a theory of the pathophysiology of schizophrenia.

I have the highest regard for Snezhnevsky's thoughtful and scholarly treatment of the problem of phenomenological precision in psychiatry, and I share his respect for the clinical method, believing with him that it is far from having exhausted its possibilities. Snezhnevsky did not say so—perhaps out of politeness—but was I right in sensing in his unspoken implications a certain critique of the disregard for the sound clinical method that has developed in many psychiatric quarters on this continent, where sound observation is too frequently shortchanged in favor of a somewhat hypertrophied psychodynamic approach? If he did imply this, we see certainly eye to eye on this issue. North American psychiatry is in need of a revival of careful and productive clinical approaches and, on this score, we can learn a great deal from European psychiatry.

May I simply state briefly that those of us on this continent who take the clinical and phenomenological aspects of psychiatry quite seriously nevertheless would not agree with much of Snezhnevsky's terminology and psychopathological orientation, which to a considerable extent have been taken over from the French schools of psychopathology, and most of which is blended with the

theoretical orientation of Pavlov. I should like to say here that while Pavlo was undoubtedly one of the greatest researchers and theorists in the field of th behavioral sciences, his clinical experience was insignificant and his clinic knowledge was largely acquired secondhand. Perhaps he would have mad a superb clinician, just as Freud might have become a first-rate experimentali if either had chosen to do so. As the matter stands, however, the domain i which Pavlov reigns supreme is *experiment* and theory, while Freud made hi mark as a *clinician* and theorist.

Both men have become immortal for their contributions to the behavior sciences. Each one has created theoretical concepts of gigantic impact tha possibly will leave his stamp on all research on the behavior of living orga isms that will be carried on in the future.

In FIGURE 1, I have expressed in diagrammatic form what I consider to b the methodological situation of the behavioral sciences in our day. The thre main streams of behavioral research move in the fields of conditioning, c neurophysiology, and of psychoanalysis. These main streams branch out, i the area of conditioning, into (1) what I have called here transcerebral classi conditioning in the Pavlovian sense; (2) the experimental modification tha is concerned only with conditioning processes within the brain itself, bypassin the rest of the organism; and (3) the considerably modified form of conditionin in which the subject is conditioned to produce the unconditioned stimulu actively instead of having it passively imposed upon him.

In the area of neurophysiology, the branches go in the direction of neur chemistry. This itself now tends to develop into neuroenzymology and in th direction of electrophysiology, which in recent years has stretched out stron feelers towards cybernetics or the science of processing mechanisms.

In the area of psychoanalysis, the branches concern themselves either wit the individual—and, in this case, usually with psychodynamic psychiatry—o with social problems, and thus would find expression in such sciences as sociol ogy and anthropology. I have indicated that I consider conditioning an neurophysiological research as being concerned chiefly with the explanatio of quantitative relationships, while psychoanalysis aims primarily at the unde standing of qualitative relationships.

Since neurophysiology has not been created *de novo*, as happened with con ditioning and psychoanalysis, both of which sprang from the conceptual inspira tion of their founders, we find that Freud and Pavlov are the two men who ar responsible for the theoretical orientation of all modern psychiatry that is no following strictly conservative lines. This may not be to the liking of th orthodox Freudians and Pavlovians, but the fact remains that these two ideol ogies have shaped today's behavioral sciences: one ideology emphasizin explanation, quantities, and causal factors, and the other stressing unde standing, qualities, and symbolic factors. Of course, many practitioners of th behavioral arts and sciences do not adhere exclusively to one ideological orienta tion or the other, but take what they consider to be the best from either.

Let us return to Snezhnevsky's stimulating paper. The author endeavor to demonstrate the physiopathological substrate of paranoid schizophrenia He claims that Pavlov's theory of the nature of schizophrenia has been con firmed by his experiments involving the toposcopic observation of cerebra

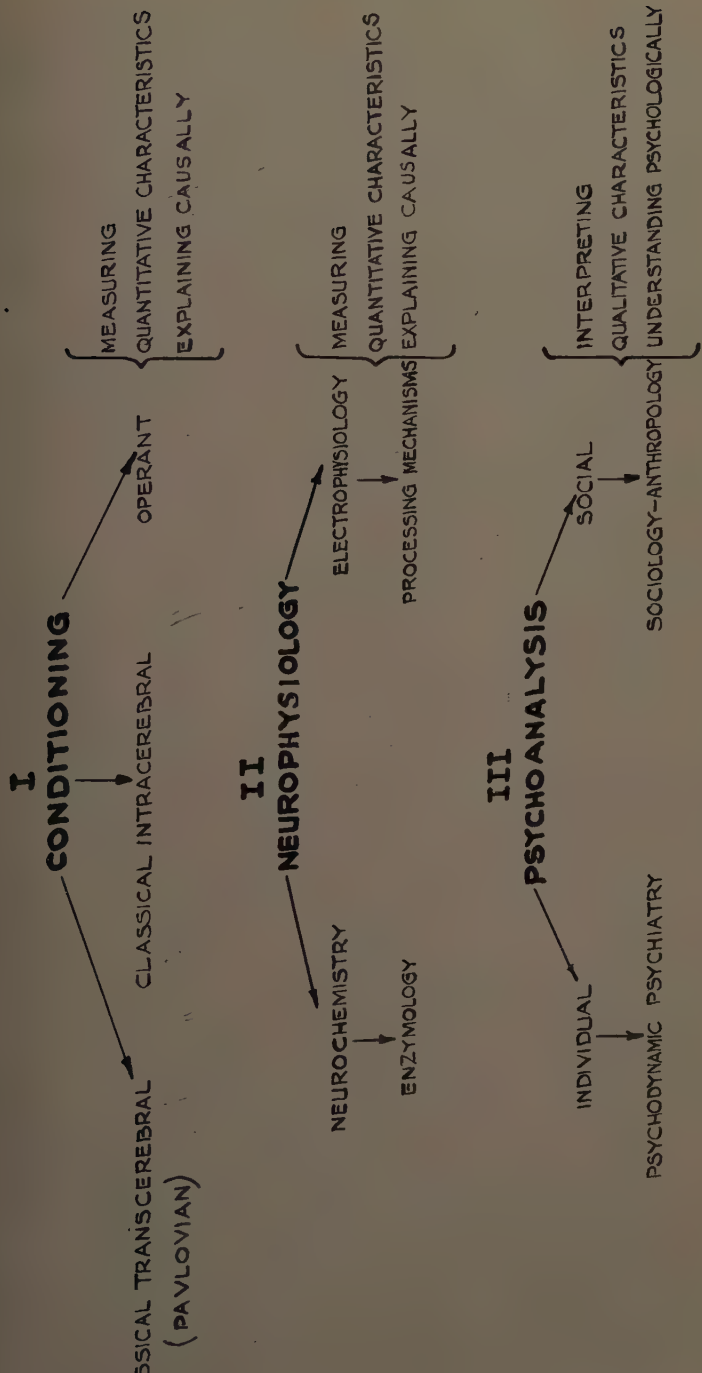

FIGURE 1. The three conceptual and procedural models of today's behavioral research.

activity following the administration of a psychopharmacological excitant (pipradrol). Let me state briefly a very simplified version of Pavlov's theory of the nature of schizophrenia for those of our United States readers who may not be too familiar with this particular aspect of Pavlov's work.

Pavlov considers schizophrenia to be a kind of chronic hypnotic inhibition. This condition develops on the basis of a hereditary or acquired weakness of the nervous system. This state of sustained inhibition is at once pathological by reducing the patient's normal activity and protective by shielding him against overwhelming stimulation. This is the first stage of what Snezhnevsky has called a chain reaction of pathological processes in the nervous system, and it is referred to as the equivalent stage. It is followed by the stage of paradoxical inhibition, during which the nervous system reacts more strongly to a weak stimulus than to a strong one. The final stage is the ultraparadoxical, during which a positive stimulus evokes a negative response and a negative stimulus produces a positive response. These stages are beautifully demonstrated in an experiment performed by Lebedinskaya: after the administration of chloral hydrate to a dog, two conditional food reflexes of different strength and a negative conditional reflex were established. In the first stage of the chloral hydrate-induced inhibition, equal amounts of saliva were excreted in response to either of the two positive stimuli. No secretion occurred after the negative stimulus. This was the equivalent stage. In the next stage, the paradoxical, there was increased salivary secretion to the stimulus of weaker strength. In the final stage, the ultraparadoxical, a response occurred only to the negative stimulus and none to the positive ones.

If I understand him correctly, Snezhnevsky feels that the altered cerebral reactions of his schizophrenic patients, when exposed to the effects of an excitatory drug and observed through the toposcope, reflect these various stages of pathophysiological disturbance with unfailing regularity. Here I am unable to follow him, for he speaks of greater complexity of symptoms and of the toposcopic picture, whereas I should have spoken of greater simplicity. He speaks often of stereotypes and, at times, refers to developmental stereotypes in the natural history of the illness. At other times he refers to stereotyped potentials in the toposcopic picture, and again refers to dynamic stereotypes in the balance of conditioned responses. Finally, there are the many stereotypes of schizophrenic behavior, such as posturing, mannerisms, and verbigeration.

I have difficulty with other concepts, too. Snezhnevsky speaks of the predominance of the second signal system over the first and of the cortex over the subcortex in schizophrenia, in which a pathological inert excitation of connections leads to the derangement of their interrelations. Is this predominance a morphological or a functional one and, if it is the latter, is it to be understood in neurophysiological or behavioral terms? What is the neurophysiological substrate of Pavlov's excitation and inhibition? Can these terms be operationally defined with the aid of neurophysiological procedures?

My admiration for Pavlov's achievement is very great, as it is for the achievement of Freud, but I fail to see that either Freudian or Pavlovian theory nor, for that matter, neurophysiological theory can do more than explain or help us to understand psychopathological phenomena after the fact, that is after they have occurred in their individual manner. We have no theory that will

enable us to predict human behavior in the way that our friends the physicists—although I have doubted in recent years whether they are still our friends!—predict the behavior of inanimate systems. Pavlov, it is true, has given us the means of predicting to a certain extent the behavior of simple animal preparations, but this does not prove that we can be certain of reducing in time human behavior and human psychopathology entirely to equally predictable dimensions.

Perhaps I simply lack faith. I must confess that I envy those fellow scientists who find no difficulty in feeling certain about things that cannot be proved scientifically, who feel certain for no other reason than that their explanations are rather plausible or comfortable or otherwise desirable to accept.

Snezhnevsky quotes Pavlov's credo in the following words: "Only by studying the physicochemical processes that are occurring in the nervous tissue shall we obtain a genuine theory of all nervous phenomena; the phases of these processes will provide us with a complete explanation of all the outward manifestations of nervous activity, the sequence in which they appear and the connections between them." Pavlov was convinced that in this way a complete explanation of nervous activity would eventually be obtained. But could he really know? Where was his scientific proof?

Snezhnevsky tells us at the end of his paper that of the two main historical directions in which psychiatry has developed—the causal and the psychologically understandable—only the former is being carried to fruition by the science that is developing today. I cannot share his belief, although I must admit that I wish I could. It would make life a great deal more comfortable for me.

I shall conclude my discussion on a facetious note. I found it very enjoyable to read through Snezhnevsky's entire paper without encountering any statistics, not even a little chi square squeezed into a footnote! North American researchers in the behavioral sciences have reached a stage of such stereotyped compulsiveness that they cannot under any condition forego the statistical ritual. It is refreshing to see that European scientists thus far have not all fallen victim to this proclivity. Perhaps I should inform Snezhnevsky of another intimate detail of our idiosyncrasies in reporting research results on this continent: we seem to have a strong masochistic tendency on this side of the Atlantic and somehow do not seem to be able to report or receive research data comfortably if there is not at least a sprinkling of negative results presented as well. Snezhnevsky reported only positive results, and I shall leave it to him either to interpret these peculiarities of ours psychologically or to explain them simply as dynamic stereotypes!

I thank Snezhnevsky for bringing to us some original and valuable research results and for providing us, through his paper, with this opportunity for a stimulating exchange of ideas.

Louis Lasagna (*Johns Hopkins University School of Medicine, Baltimore, Md.*): It is a privilege to be asked to discuss the work of one of our distinguished Soviet colleagues, and to share these pages with such distinguished American Pavlovians as W. Horsley Gantt and Howard S. Liddell. I hope I may be pardoned for taking a special pride in Gantt's work, since for so

many years he brought, through his research, honor and distinction to the institution in which I now work. I regret that, like most Americans, I speak few foreign languages, none well, and Russian not at all. I also regret that my own limitations will render the brief comments I shall make a small contribution to these proceedings, despite the fact that A. V. Snezhnevsky has provided us with a provocative paper. Snezhnevsky has rightly stressed that no single approach—physiological, biochemical, or psychological—is likely to solve all the problems of psychosis. However one might also stress another obstacle to progress: the barrier of confining theoretical constructs. Whenever a giant figure appears on the world scene he presents the future with the possibility both of gain and of danger: the gain deriving from his contributions and the danger from a too worshipful approach to his concepts and data. Freud and Pavlov have affected our scientific climate for all time but surely, if we are to progress, we must go beyond the concepts of past heroes. Thus in the United States one could marshal little support for Snezhnevsky's statement that Pavlov's conditioned reflex model has provided "the principle used to classify psychotropic agents." Similarly, I wonder if one may not get into a dangerous bind by formulating excessively detailed and rigid theories as to the development of psychiatric illness. One might question whether we ought to categorize schizophrenia as a syndrome of "automatically evolving pathological chain reactions," lest we adopt inappropriate and pessimistic therapeutic positions and become prisoners to a possibly incorrect and excessively restrictive theory.

Before going on to discuss the specific technique Snezhnevsky has provided for us here, I should also like to make a plea for the international standardizing of psychiatric nomenclature. Psychiatry has enough problems of communication without creating others by an appalling inconsistency of terminology in different sections. A recent review of the world literature on imipramine impressed strongly upon me the alarming discrepancy from country to country in the labels affixed to psychopathology.

Snezhnevsky, needless to say, is dealing with a most fundamental problem. Whether one believes schizophrenia to be "functional" or "organic"—and I confess to difficulty in being certain of the validity of such a distinction—scientists would presumably agree that disturbed behavior is intimately tied in with disordered function of brain tissue. Since the electrical activity of the brain is correlated in some way with cerebral functioning, it should follow that one ought to be able to differentiate easily, by the EEG, between normal and grossly psychotic subjects. However, standard electroencephalography has been extraordinarily disappointing in this regard. A natural conclusion would be that limitations in technique have been responsible for the low resolving power of the standard EEG. In recent years, attempts to go beyond standard techniques have been reported, with promising initial results, and I hope that some of the more knowledgeable contributors to this monograph will comment on these techniques.

What of the procedure described here? In the short space available to him, Snezhnevsky has not been able, of course, to present us with all the information he would have liked to present and that we should like to have. For

example, one would like to know how many "bioelectric mosaics" have been obtained in normal people? How many in psychotic patients? How replicable is a given pattern from day to day in the same patient? Does the technique utilize spot size in addition to spot intensity, as suggested by some of the pictures illustrating his paper? (One might prefer to use spot size whenever possible, since it is visually easier to follow differences in size than differences in intensity.) Has Snezhnevsky experimented with films of varyingly rapid exposure to see whether more information could be obtained from films taken at a faster rate? What of the quantification of the technique and the communication of results to others? In a method such as is here described, in which one relies so much on changing patterns over time, it would seem that the presentation of data in the form of individual frames, such as Snezhnevsky utilized, would give a totally inadequate picture of what is taking place. Have computers been used to help deal with the masses of data obtained? Is the bioelectric mosaic so highly correlated with clinical diagnoses that either one can serve as a predicter of response to drugs, or are there interesting and perhaps useful discrepancies?

Some of these questions are almost certainly answerable at present from Snezhnevsky's work; for others, much more work will probably be required. We all look forward to the opportunity of seeing Snezhnevsky's fascinating work reported in full in the near future.

Snezhnevsky: I shall answer the comments that have been made by discussing first, electroencephalography; second, the question of statistics; third, the stereotype of development; I shall conclude by making a few remarks about Pavlov and Freud.

First may I express the hope that my colleagues in psychiatry in the United States will show some interest in the method of Livanov and Ananyev whose book *Electroencephaloscopy*[1] was published in 1960 in the Soviet Union on the method of electroencephaloscopy. This book contains the first data available on this method. I think that this book would be of interest to psychiatrists and electroencephaloscopists in the United States, and that it would do them good perhaps to get acquainted with its contents, which would not present much difficulty in so far as translation is concerned.

In the clinic and in the laboratory of the clinic where I work, we examine patients by a parallel method using both electroencephalography and electroencephaloscopy. These two types of investigations have been used for three years now, and I should tell you in all frankness that we consider that electroencephaloscopy gives better results, in so far as it gives a more complete picture of the variations and changes in the activities of the brain in persons suffering from psychiatric diseases.

This opinion, indeed, has been shared by one of my United States colleagues, J. Romano, who visited my laboratory. I was able to show him a film of various kymograms showing the pathology and development of the conditioned reflex, recorded by means of frames through electroencephaloscopy, which thus could be projected and seen on a screen.

In these pages I was able to show but a few figures. One must, however, bear in mind the fact that when we study a patient, when we investigate his

case, we take tens and even hundreds of meters of film at the rate of 24 frames per second.

May I point out that at the moment Livanov is combining his electroencephaloscope with an electronic computer. This would make it possible to give information that will be not only more accurate but also (I wish to stress this point) much more complete, because it will provide us with the correlation between the intensity of each biopotential and the intensity of the other 50 and, in some cases, the other 100 biopotentials. This will enable us to give a mathematical expression for all pathological deviations.

The data on bioelectric mosaic of schizophrenic patients were compared with the bioelectric mosaic of healthy individuals, and with the reaction of the latter to Meratran and chlorpromazine. I have demonstrated here the most typical kymograms selected from the thousands of kymograms obtained by N. A. Gavrilova, N. Ia. Belen'ka, and F. A. Leibovitsch of the laboratory staff in the investigation of approximately 100 schizophrenic patients.

Furthermore, on the question of statistics, may I point out that, as regards the development of schizophrenia and the investigation of the dynamics of schizophrenia, work has been carried out in my clinic by my associates and myself for the past 10 years, that is to say, since 1951; during this period we have had under constant observation 1,244 patients suffering from schizophrenia.

Moreover many of those 1,244 patients suffering from schizophrenia had been sick earlier, and the development of the disease in them, therefore, could be followed not only by their present clinical history but also by their previous history of disease.

This accumulation of combined data has been published in an article in the *Zhurnal Nevropatologii i Psikhiatrii imeni S.S. Korsakova*,[2] in the issue of September 1960. It should be added that individual data have been published since 1951.

In the hospital where my clinic is situated, there is also constant central control of investigations.

The observations to which I refer make it possible to affirm that one can extrapolate the stereotype of development—that is to say, the general characteristics of the course of development—and that this is completely different in the four types of schizophrenia we have studied: paranoid schizophrenia, catatonic schizophrenia, simple cases of schizophrenia, and recurrent schizophrenia.

The characteristics are so different in these four types that it has become easier to predict the development of the course of the disease.

Variations in the stereotypes of the development of the disease in all its different forms, which I have just enumerated, seem to make it possible for us to affirm that this is indeed a unified group of diseases, but we dare not do so as yet.

The stereotype of development naturally presupposes that there are individual deviations. These individual deviations vary greatly, but they are all to be found within the framework of this stereotype of development. For instance, it is known that paranoid schizophrenia is characterized by obsession

paranoid disturbances, and depersonalization; when a case of schizophrenia begins with one of these three conditions we have been able to predict, as the disease progresses, the extent to which it will develop into a paranoid schizophrenia of the Clérambault-Kandinsky type.

It should also be pointed out that the stereotype framework to which I refer is maintained until the very end of the development of the disease.

I should like to emphasize a point mentioned above: investigations by means of electroencephalography and, especially, by means of electroencephaloscopy have shown that there were wide variations in the level of the bioelectric mosaic, variations that pertain to the different forms of schizophrenia. For instance there are, as may be seen from the figures I presented with my paper, great differences between the paranoial and depressive types of schizophrenia.

Thus the clinical differences that we were able to observe are, in fact, due to pathological differences, and are also correlated with the disturbances of central nervous activity.

Pavlov, in the course of his life and work and in the course of 20 years of experience with those questions, often dwelt at great length on paranoid schizophrenia, as well as on the paranoial and paraphrenal stages. He tried to explain the paranoial stage, the one in which there are delusions, by the existence of inert foci of nervous excitation. Our investigations have confirmed that hypothesis, but have thrown a somewhat slightly different light on it. The inert state does exist, but the foci do not yet exist in so far as we were able to determine; they arise only after the application of stimuli or later, when the patient has reached the stage of automatism, hallucination, or still greater disturbances in the activities of the cortex. This situation leads to activization of the inert foci of excitation, and it should be noted that the growth of these foci is always, without exception, correlated with the appearance of a worse clinical picture of the patient.

This is the general trend that I have desired to make clear.

There is a greater disorganization that takes place in the terminal stages of schizophrenia; yet this greater disorganization is primarily of a physiological character, because treatment by many derivatives of phenothiazine has led to great improvement in the patients even (I stress this point) in the terminal stages of schizophrenia.

I agree with Lehmann (this is a question that is touched upon by other contributors to this publication) that very often misunderstandings between us are due to the tremendous variety of terminological differences in our fields of activity.

Quite recently in Geneva, Switzerland, R. Felix from Washington, D. C., spoke before the Mental Health Section of the World Health Organization of the United Nations of this difference in terminology and expressed the hope for a standardization of terms. I believe, however, that such standardization could only be gradual. It could not take place all at once because in many cases the difference in terminology is due to our different respective positions and also to some extent to the history of psychiatry in the various countries involved.

I refer now to the distinction to be drawn between Freud and Pavlov's un-

derstanding of psychoses. The followers of both Freud and of Pavlov, whe[illegible] they studied and explained the initiation of psychoses, attached much impor[illegible] tance to harmful social factors and also to psychogenic facts. There is, i[illegible] fact, no difference of principle at this particular stage.

The differences arise and become clear at the later stage. The followers o[illegible] Freud consider that the inner formation of various neuroses and psychose[illegible] that is to say the pathogenesis itself, is again of a purely psychological characte[illegible] and that it does not depend upon the activity of the brain.

The followers of Pavlov, on the other hand, consider that the inner formatio[illegible] of neuroses and psychoses, the pathogenesis itself—and the question of whethe[illegible] the neuroses or psychoses are psychogenic or not does not matter in this case— is always purely physiological and that it is always due to disturbances of th[illegible] central nervous system.

However simple or complex our ideas may be, they are also always based o[illegible] the conditioned reflexes of nervous activity; similarly, however simple or com[illegible] plex our psychic disturbances may be, these too are always based on the highe[illegible] nervous processes, and that is the gist of the difference and of the remarks [illegible] have desired to make here.

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NATHAN S. KLINE (*Rockland State Hospital, Orangeburg, N. Y.*): Snezh[illegible] nevsky's last remark fits in with my own point of departure, which will b[illegible] very brief: namely, that both the Pavlovian and the Freudian schools are to[illegible] insistent that all types of varieties and kinds of behavior must be explaine[illegible] exclusively in a particular universe of discourse, the one the physiologica[illegible] universe and the other the psychological. I think there are occasions whe[illegible] both are needed.

The great difficulty, I find, with the Pavlovian approach is not only that i[illegible] is within a single universe of discourse but that primacy is given to the cerebra[illegible] cortex as the controlling organ in all cases. I think this primacy is true i[illegible] certain cases only. There are other times when the cerebral cortex may me[illegible] diate or be involved in the causal chain but may not be primary, and there ar[illegible] probably other occasions when it merely reflects changes that occur elsewher[illegible] in the organism, but it does not directly originate or participate in the causa[illegible] chain itself.

As to the particulars of the experiments, it is remarkable that, despite di[illegible] vergences of theories, there is a parallelism in respect to interest and focus o[illegible] laboratory work.

One of the workers in my hospital, George Simpson, is carrying out som[illegible] experiments highly parallel to those of Kerbikov.

GEORGE M. SIMPSON (*Research Facility, Rockland State Hospital, Orangeburg*[illegible] *N. Y.*): Kerbikov certainly has given a stimulating paper that, in addition t[illegible]

the information it contains, highlights many differences of approach to the subject of schizophrenia in the Soviet Union as compared to other countries. I am thinking at the moment of the initial conceptualization in the Union of Soviet Socialist Republics, where even the collection of data in a difficult subject such as schizophrenia is already associated with a preformed hypothesis; in the United States and other countries there seems to be more concern in psychiatric research with peripheral events in the collection of data and, of course, there are many more hypotheses. For example, I feel certain that few workers in this country would relate immunological reactivity and catatonic states directly via the central nervous system. On the other hand, I should be surprised if they did not think they were related.

No one would disagree that the immunological mechanisms are components of homeostasis, but whether one would agree that homeostasis is controlled, at least by implication, only by the nervous system and would, therefore, postulate that immunogenesis is under the same control, is a somewhat different story. However, leaving that aside for a moment, I shall discuss some work my colleagues and I have done in a related field and also mention other work done in the West pertaining to Kerbikov's paper.

Kerbikov discussed the role of chloropromazine as an allergen, but it should also be said that it can act as an antiallergen. Discussing this, he mentions the relatedness of allergy to immunological activities. Our own work has been concerned with allergy, particularly with histamine sensitivity. We have been able to show that chronic schizophrenics as a group show a diminished response to injected histamine, as measured by wheal formation. The interesting finding in our work[4] is that chronic schizophrenics, as a group, differ not only from a normal control group but also from acute schizophrenic patients. This, we feel, indicated that chronicity of the illness has in some way an effect on the subject's ability to act allergically. This being true, one wonders, of course, about the patients chosen in Kerbikov's group, that is, their ages and length of their hospitalization. Whether this diminished response to histamine is a peripheral or central action we cannot say at present, but certainly we are not willing at this stage to implicate only the central nervous system. The causes of this phenomenon, although it is ultimately under nervous control, can be explained at a lower level. Thus schizophrenics have been reported to have an elevated blood histamine level and a process of autodensensitization has been suggested; drawing from both camps one could say that the diminished ability of the schizophrenic to react homeostatically has resulted in the diminution in size of the histamine wheal.

On the other hand, in the triple response of Lewis[8] it was initially presumed that the flare was mediated via an axon reflex without suprasegmental involvement. However, recent work by Cooper[2] suggests that the spreading flare may be dependent on the function of diencephalic centers; thus an intact peripheral nerve is required to mediate the reflex, but lack of diencephalic control as in decerebrate rigidity may abolish the flare. Again, in complete cord transections, the flare component is found to be diminished but the actual wheal remains the same. This would suggest, therefore, that the phenomena that we are studying are not directly under the control of the nervous system.

Unfortunately there is no unanimity on the subject, for Bereston[1] reported

that both the flare and wheal are diminished in the centrally denervated skin of the paraplegic, and there the dichotomy rests.

To go back to our own work, the allergic manifestations were found to be altered by some psychopharmaceuticals. The drugs tested were meprobamate, prochlorperazine, chlorpromazine, imipramine HCl, and reserpine. The numbers in each group were not large, but there was a statistically significant alteration of skin sensitivity in patients receiving imipramine HCl and prochlorperazine. This again could be related to a central or peripheral effect; I favor the latter, for the following reasons. Recent investigations in Switzerland[5] have shown successful use of imipramine HCl in various allergic conditions, with considerable improvement frequently taking place in the first hour. I myself have treated a small but significant group of cases of hay fever and allergic rhinitis with imipramine HCl and have been surprised at the number of people who were *relieved within one hour*. One does not expect a central or antidepressant effect for at least several days, and this rapid onset of the antihistaminic effect suggests that the drug has a peripheral as well as a central action.

Among other workers in the field, Vaughan and his co-workers[7] have shown that the schizophrenic group as a whole was more variable but, as a group, it had lower serum antibody titers in response to injected pertussis vaccine. Freedman *et al.*,[3] in discussing their findings and those of Vaughan, suggested that this diminished ability to develop sensitization or antibodies may indeed be related to altered central nervous system activity. Further evidence in favor of the above could be adduced from Stanton *et al.*'s work,[6] albeit on the rat, that destruction of the temperature-regulating centers causes alterations in the antibody response.

To return more directly to Kerbikov's paper, I should again wonder about chronicity. I should be interested to know if he finds that the total white cell count is apt to be diminished in chronic schizophrenia and if he also finds alterations in the albumin-globulin ratio in chronic schizophrenics as reported in the United States. This would be particularly interesting in relation to the group of patients reported here who, it is stated, had an increased antitoxin level before treatment. One wonders what effect an initial elevated globulin fraction would have on the development of other antibodies containing globulin.

I do not feel too happy that, because the difference in immune response depended more upon the clinical status of the patient than the nature of the antigen introduced, this proves the dependence of the immune response on the central nervous system functional condition. Again, it is stated that six months after primary vaccination those patients whose condition did not change were revaccinated and that the mean globulin agglutination titers were not as marked on this occasion. Therefore it may be stated that in revaccination the immune process is less dependent on the functional state of the central nervous system. This, I feel, requires further explanation.

"The greatest change of immunological response . . . was found in stuporous patients. . . . [It] is indicative of the spread of inhibition into the brain stem," and therefore the subcortex is important, says Kerbikov. This leads to the neat choice of parkinsonism for testing the hypothesis. However I question

the reasoning involved and certainly the statement that "the data obtained in this study confirm the assumption that subcortex dysfunction is more important than cortex dysfunction in the central regulation of immunity processes."

In summary, Kerbikov presents a refreshing attempt to elucidate many of the known abnormalities in schizophrenia that certainly meet in the middle but diverge at the ends, from work carried out in this country. His work has the value of being simple and highly quantitative.

From another point of view, the cooperation of different disciplines for a period of five years on a problem such as this, and the larger number of subjects used, commands respect.

Despite the difference in conceptualization, this seems to me the most thorough study in this area yet carried out. For this I thank him.

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Fred A. Mettler (*Columbia University College of Physicians and Surgeons, New York, N. Y.*): Elsewhere in these pages Gantt refers to fads in psychiatry. Such fads not only exist in other areas of medicine but also in research. The period of perhaps four or five decades ago saw, as does the present, great activity in institutions caring for psychiatric patients and others located on what was then euphemistically called Welfare Island, in East River, New York, N. Y. Such activity, which later died down, was concerned with the study of the development of immune reactions. The impetus for this work came from the New York City Health Department, which was charged with the still new task of building up immunity, especially in the child populations that were confined to the city institutions.

At that time, a large body of data was developed that is applicable to the present considerations. In the first place, it became apparent that it was extraordinarily difficult to get base lines for the population samples. In the second place, the range of variation in the response of different individuals in the studied population was very great. Finally, it became necessary to remain on the alert to artifacts that often produced aberrations that appear in certain groups of data in this kind of work. It is to be hoped that when this

monograph becomes available Kerbikov's material will be provided in a form that will make it possible for the immunologists to extricate the critical factors.

I now address myself to something Kerbikov did not say. I emphasize the words *did not* because I do not want my Soviet colleagues to get the impression that what I am saying at this moment has any relationship to anything they said. My reason for calling attention to forbearance on Kerbikov's part is because I have repeatedly been disturbed in reading these pages by the tendency to employ *ad hoc propter hoc* reasoning.

Let me call attention to the kind of situation I mean. A table is presented in Kerbikov's contribution to this monograph that demonstrates an extraordinary similarity between the behavior of two groups of patients, one with schizophrenia and the other with parkinsonism. Those of you who are familiar with my work might expect me to jump with glee and joy in encountering such a correlationship, but I do not jump with either glee or joy in this connection because I think it illustrates the kind of trap into which we are all too happy to allow ourselves to fall.

Kerbikov will have to correct me on the identification of portions of his TABLE 2.

KERBIKOV: The middle line is the oligophrenic group, the upper one is the schizophrenic group, and the lowest one is the Parkinson patients.

METTLER: Kerbikov himself very carefully provided us with a safeguard that should prevent easy error in correlating the two latter abnormal conditions. He pointed out that the parkinsonian patients were postencephalitic. This makes a great deal of difference. Without knowing this one might be tempted to make a correlation between the behavior of schizophrenics and parkinsonians, but when the word "postencephalitic" is introduced we immediately become aware that the latter patients must have pathology in a great many places other than in extrapyramidal mechanisms. Encephalitis, of course, hits the whole base of the brain; it hits the hypophysis too.

My dear colleague Kline made a comment implying that Kerbikov had attributed his findings to disability of the nervous system. I did not understand this from what Kerbikov said. All I understood was that he had presented some data. While it is not often done, I should like to thank Kerbikov for the things he did *not* say; such reserve is commendable. I hope it is a physiological process that indicates a highly infectious condition for which no immune body will ever be discovered.

ENOCH CALLAWAY III (*The Langley Porter Neuropsychiatric Institute, San Francisco, Calif.*): I shall make some very brief remarks on Kerbikov's paper, since the work I am mentioning is not my own but that of Jeffrey Fessel of the laboratories at the University of California, San Francisco.

Fessel first became intrigued by the high incidence of psychosis in patients with systemic lupus erythematosus. Fessel screened a large population of psychotics with an immunochemical test for systemic lupus erythematosus and found a greater-than-expected number of positive sera. Examining these patients, however, he found no more than the expected number of lupus patients. Similar screening was conducted for the so-called rheumatoid arthritis factor in the sera and again a large number of positives were found, although no more than the expected number with clinical diseases.

Thus the psychotic population tended to have larger-than-expected numbers of patients with sera positive for the lupus factor and the rheumatoid factor, but without clinical disease.

This has led Fessel to continue studying the sera of psychotic patients, and he continues to find peculiar, unusual serological patterns by both immunochemical and electrophoretic tests. Again, it is too early to make any statements about what this may mean, but I wonder if Kerbikov has speculated on the possibility that some of the changes in schizophrenia may be due to immunochemical and connective tissue problems, rather than that the immunological changes are a result of central nervous system change.

O. V. Kerbikov: I have been asked whether in the Union of Soviet Socialist Republics there have been any new studies conducted along the same general lines that were investigated by G. Y. Malis. For several years now, Malis has been carrying on investigations in this particular field; the purpose of his studies is to establish a virus etiology for schizophrenia.

His studies have been summarized in a monograph[1] he published early in 1959.

He uses a special technique in his investigations involving the absorption of viruses by microbes. All microbiologists apparently do not appreciate the importance of this absorption relationship, which is so difficult to translate. There have been no additional disciples in the school of Malis, in so far as I know. On the contrary, the tendency has been in just the other direction. The hope of discovering a virus as a causal factor in schizophrenia has been rapidly diminishing.

Today there has been a new tendency in these studies that is reflected in the search for autoantigens. Albumin organisms, if they do not undergo any modification, may acquire the characteristics of autoantigens; this is of great importance. The comments on my paper were very interesting, but because of space limitations I ask you to excuse me for the brevity of the answers that I shall give.

Kline began his comments with a confrontation of Freud and Pavlov. I had a great deal of difficulty in refraining from stepping into the arena in this discussion. If I had, we should have run the risk of engaging in a heated and excessively prolonged discussion.

I should like to say simply that psychism is, of course, a function of the brain and that when psychism is disturbed, the brain function is affected.

Certain interesting studies that are being carried on under the guidance of Kline are rather at variance with our own findings.

One of the conclusions I drew in my report was that the immune reactions found in psychic patients are unbelievably complex. Even in using different methods and various techniques, the results obtained still are divergent. At present we are also studying allergic activity in schizophrenics.

For the time being we feel that allergic reactions, particularly serum infections, are more difficult to elicit in schizophrenics than in other types of patients.

I shall conclude by referring to the remarks of Mettler, who thanked me chiefly for things I did not say. I am very happy to take cognizance of his

gratitude and I consider it to be a positive reaction on his part to my presentation.

The main and chief danger facing all investigators in the field of schizophrenia at the present time is that of saying more than they actually know.

I just said I was afraid of saying more than I knew! I have just been asked what role we attribute to thyroxine. I do not engage in such studies and am unable to answer that question.

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Part VI. Inhibition

THE INITIATION AND LOCALIZATION OF CORTICAL INHIBITION IN THE CONDITIONED REFLEX ARC

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The coordinating role of inhibition—a role of the utmost importance in the integrative activity of the central nervous system, particularly its higher divisions—was demonstrated and described in detail by the classical neurophysiologists: Ivan M. Sechenov, Charles Sherrington, Ivan P. Pavlov, Nicolai I. Vedensky, and their successors. The facts and theoretical propositions of Pavlov and his pupils pertaining to another important role of inhibition in the vital activity of the same system—namely, its protective and restorative role—are also well known. In addition, modern physiology also has available to it a large body of factual data relative to the regular patterns of the rise of inhibition in nervous structures, its interaction with excitation, its dependence on various kinds of factors, and the diversity of its manifestations. However, in spite of the unceasing and even accelerating progress of our knowledge about inhibition, many of its aspects still remain to be worked out, and neurophysiologists, following Pavlov, still refer with some bitterness to the "confounded problem" of inhibition.

Included among the questions pertaining to this problem that have not been sufficiently studied and remain largely unanswered is the question of the initiation and localization of various types of cortical inhibition in the elements of the conditioned reflex arc. This paper is concerned with just this question, and contains a brief exposition of several new facts obtained by my colleagues and myself, together with theoretical propositions that derive in large measure from these facts.

The question of the initiation and localization of various kinds of cortical inhibition in the elements of the conditioned reflex arc has attracted the attention of investigators throughout the entire period of development of the theory of higher nervous activity. Most of this attention has been paid, and continues to be paid, to the development and localization of conditioned inhibition: that is, the type of inhibition that is specific to the cortex and its most important activity. Until recently there were, in the main, two opposing points of view respecting this question. I refer to (1) the position first set forth by Babkin[9] and Zelyony,[25] and later championed by Pavlov himself, that conditioned inhibition is initiated in the cortical nerve cells of the focus of the conditioned stimulus (CS in FIGURE 1); and (2) the view advanced by Perelzweig[17] and Kasherininova,[10] and later upheld by P. K. Anokhin,[1] B. I. Khodorov,[13] and others, that conditioned inhibition is initiated in the nerve cells of the focus of the unconditioned stimulus (US in FIGURE 1). The first viewpoint is supported chiefly by the well-known fact that conditioned inhibition is irradiated from the nervous structures of any one conditioned reflex to the nervous structures of other conditioned reflexes of the same type and, at times, even to those

of other types (that is, by the fact that this inhibition spreads to other related and even unrelated conditioned reflexes). In behalf of this point of view, A. I. Roytbak[18] cites his own recent data showing that when a conditioned reflex is extinguished, the character of the electrical reaction of the cortical focus of the conditioned stimulus in response to the application of this stimulus changes markedly. No significant direct facts have been invoked on behalf of the second point of view, but its correctness is usually argued on indirect grounds, especially on those pointing to the unsoundness of the opposing viewpoint—that is, the first viewpoint—(critics note, for example, the reception [perception] of the stimulus of the inhibited reflex and other factors).

In addition to these two long-standing points of view, other opinions about this question have also been expressed. In this connection I must mention

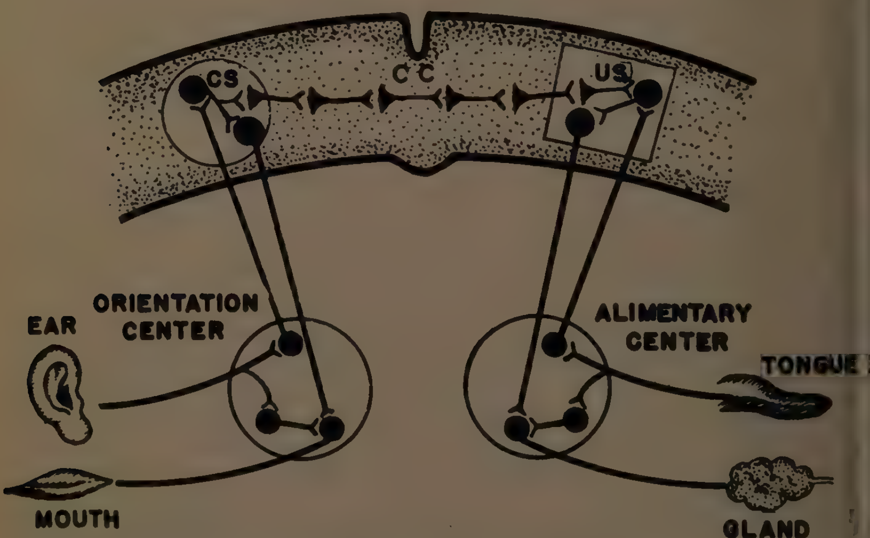

FIGURE 1. Scheme of the conditioned reflex arc. Key: CS, conditioned stimulus; US, unconditioned stimulus; CC, conditioned connection.

especially the proposition developed by P. S. Kupalov and his co-workers,[14,15] that conditioned inhibition develops simultaneously in the cells of the foci of both the conditioned and the unconditioned stimuli. Furthermore, J. M. Konorski[12] has recently developed the point of view that cortical inhibition is a manifestation of the activity of special inhibitory structures, which exist apart from and in parallel with the structures of excitation at the cortical level, in somewhat the same way that they exist at the subcortical, spinal, and other levels of integration in the central nervous system. Finally, my co-workers and I have also expressed some thoughts on the initiation of conditioned inhibition and the elements of the conditioned reflex arc.[4,5,6] The essence of the point of view that we have developed reduces to the concept that conditioned inhibition is initiated primarily in elements of the conditioned *connection* itself (CC in FIGURE 1), which we represent as a chain of internuncial neurones, and not in the cells of the foci of the conditioned or unconditioned stimuli, as

the advocates of all the other viewpoints believe. We acknowledge, however, that when inhibition that has been initiated in elements of the conditioned connection becomes significantly deepened, it may subsequently encompass also the cortical nerve elements of the foci of both the conditioned and unconditioned stimuli.

What facts and arguments lie at the basis of this viewpoint, to which, from all indications, certain other Soviet scientists—as for example, G. P. Skipin,[20] F. P. Maiorov and his co-workers,[16] and others—are at present inclined to lend their support?

For purposes of giving an easily understandable account of the materials and arguments pertaining to this question we are discussing, and to make it somewhat easier to apprehend them in relief form against the canvas of space and time, I think it is desirable to present a preliminary schematic representation of the conditioned reflex arc as we conceive it. This is essentially a reproduction of the scheme that we presented more than 20 years ago, somewhat modified in the central portion in accordance with the problem that interests us at the moment. Furthermore, before we go on to an account of the actual facts and arguments in behalf of the point of view I wish to defend, I should like to point out that some of these facts and arguments are of an indirect character; that is, they are directed toward proving the fact that conditioned inhibition is not initiated in the cortical focus of the conditioned stimulus or in the cortical focus of the unconditioned stimulus. Only some of these facts and arguments can be regarded as direct justification for the point of view that we are developing about the question under discussion here.

For the sake of completeness of our account and in order to preserve the chronological sequence, it is especially desirable that we refer to facts that have been known for a long time: facts that other authors have also cited repeatedly in connection with the question of initiation of conditioned inhibition in the elements of the conditioned reflex arc. I have in mind the fact, already mentioned earlier, of the reception (perception) of the conditioned stimulus and the reaction to it following inhibition of the positive conditioned reflex (such as, after extinction, differentiation, and delay). This fact unquestionably indicates that inhibition initiated under such circumstances in the conditioned reflex arc and leading to the blocking of conduction of excitation through it is localized not in the cortical focus of the conditioned stimulus (CR in FIGURE 1) but somewhere in the elements of the arc that follow. This is obviously also indicated by facts pertaining to the different course of the extinction or differentiation of different components of the same conditioned reflex. I refer, for example, to extinction or differentiation of the salivary and motor components of the alimentary conditioned reflex. Everyone knows that often one of the components of a conditioned reflex will be completely inhibited while the second continues to be elicited for a long time. Among the facts that have been common knowledge for many years and that are of definite interest from the standpoint of the question we are discussing here is the fact that the unconditioned reflex does not change significantly upon inhibition of the conditioned reflex, by extinction, differentiation, or some other means. It has also been found that conditioned reflexes of the same type that result from other stimuli are retained, sometimes even without perceptible changes in these reflexes. From these facts we may conclude that the cortical focus of the unconditioned reflex

(US in FIGURE 1) also cannot be regarded as the site of initiation of conditioned inhibition.

In addition to the facts mentioned above, which have been known for a long time from the work of many investigators, we also have available the findings obtained by my co-workers and myself in the course of several years, which are in some ways more intimately related to the question of the initiation of conditioned inhibition in elements of the conditioned reflex arc. A brief description and interpretation of these facts are given below.

For many years my colleagues and I have systematically investigated the problem of the so-called "trans-switching" in conditioned reflex activity.[3,4] The essence of this problem is that it is possible to give a single indifferent stimulus two different signal values at the same time: for example, alimentary and electrodefensive, positive and negative, and short-delay and long-delay. This is done by reinforcing the stimulus differently in two different experimental conditions or situations (in two different rooms, at different times of the day, or by two different experimenters). For instance, we may try reinforcing with food in one situation and with electrical stimulation in another situation, reinforcing immediately in one situation and after a period of delay in another, or reinforcing in one situation and not reinforcing in another.

It is not my purpose here to set forth in full the data that we have obtained and our theoretical positions on this problem. I shall only point out that in this large amount of experimental material there are data that have an intimate relationship to the question of the initiation and localization of conditioned inhibition in elements of the conditioned reflex arc. I shall present them here in a concise account.

Let us begin with the description of the very first, highly instructive experiments of my colleagues, F. M. Shitov and V. V. Yakovleva.[19] Shitov, in morning experiments on dogs, combined a metronome beating at 120 beats per minute with food and produced an alimentary conditioned reflex to it; Yakovleva, in experiments conducted during the afternoon in the same room and on the same dogs, combined the same stimulus with stimulation of one of the animal's paws with an electrical current and produced an electrodefensive motor-conditioned reflex to this stimulus. The metronome thus assumed two signal values for the animal: a food signal value and an electrodefensive signal value (FIGURE 2). However, under concrete testing conditions, as a rule, only one of its signal values was manifested, the other remaining in an inhibited state. In the morning experiments, the metronome evoked only a food-conditioned reflex; in the afternoon experiments, it elicited only the conditioned electrodefensive reflex. It is interesting to observe that when both experimenters conducted an experiment together, both signal values were manifested: that is, the conditioned stimulus evoked both alimentary and electrodefensive conditioned reflexes although in a rather irregular fashion, to be sure.

These early data of ours are similar to facts obtained comparatively recently in my laboratory by M. I. Struchkov,[21-24] who developed two conditioned reflexes of different types: an alimentary conditioned reflex to the sound of a buzzer, and an electrodefensive conditioned reflex to a tactile stimulation of the skin. When these reflexes had assumed a considerable degree of clarity and stability, Struchkov went on to perform parallel experiments on the same

animals in another room, radically altering the character of the experiment. Specifically, in the new room he combined the tactile stimulation of the skin with food and the sound of the buzzer with electrical stimulation of the paw. Ultimately, the dogs handled even this highly difficult problem. After one phase of a double conditioned reflex reaction to each conditioned stimulus and another phase of gradual increase in the magnitude of adequate reactions and decrease in the magnitude of inadequate reactions to each stimulus in this room, the animals reached a point at which, in the one room, the buzzer produced only a conditioned food reflex and the tactile stimulus only an electrodefensive

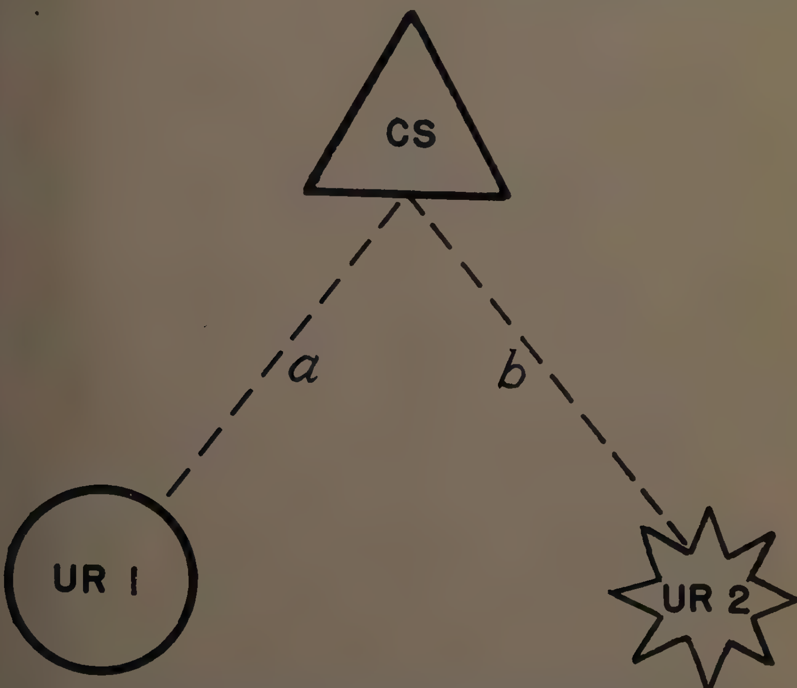

FIGURE 2. Scheme of single switching. Key: CS, conditioned stimulus; UR 1, unconditioned reflex No. 1; UR 2, unconditioned reflex No. 2.

conditioned reflex, while in the other room the buzzer evoked only an electrodefensive conditioned reflex and the tactile stimulus only a conditioned food reflex (schematic portrayal in FIGURE 3).

It seems to me to be clear from these facts, discovered by Shitov, Yakovleva, and Struchkov, that the manifestation of only one of the two conditioned reflexes of different types to the same stimulus in different situations and the suppression of the other conditioned reflex is the result of the development of a process of inhibition in those elements of the arc of the conditioned reflex that are, as it were, suppressed by the design of the experimenter. For it is clear from these facts that this inhibition is localized not in the focus of the conditioned stimulus (since in each room the stimulus evokes one of the conditioned reflexes) nor in the foci of the unconditioned stimuli of different types

(since, according to Struchkov's data, in each room and in each experiment it is possible to produce both alimentary and electrodefensive conditioned reflexes). By elimination, therefore, we arrive at the conclusion that inhibition in the instances described above is initiated and is localized in the nerve elements of the conditioned *connection* itself.

It is not without interest to note that the two conditioned reflexes of different types produced in response to one and the same stimulus are in antagonistic reciprocal relation to each other. Inhibition of an active conditioned reflex—that is, one functioning in a particular situation—to some stimulus (whether by extinction, by the influence of an extraneous stimulus, or by other means) involved automatic disinhibition of the inactive "partner" conditioned reflex

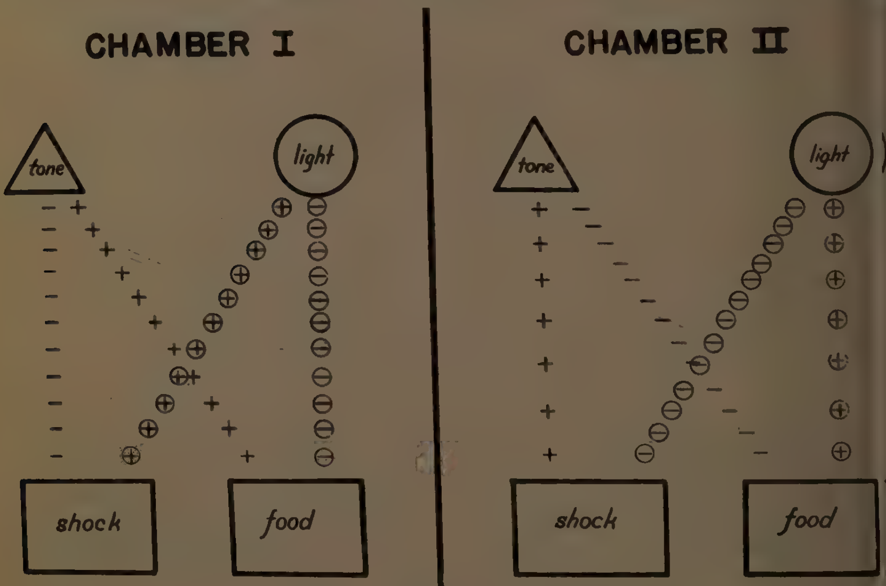

FIGURE 3. Scheme of double switching.

to this same stimulus in the situation. This highly interesting fact, which has been repeatedly verified, obviously testifies further to the correctness of these conclusions about the development of inhibition in the structural element of the conditioned connection itself.

From the standpoint of the question under discussion here, the results of experiments on trans-switching of conditioned reflexes of a single type, but with an opposite functional sign, are also of great interest. I refer to the results of F. P. Shitov and V. A. Vamyatina (unpublished data, 1938), which in essence consisted of the following. One experimenter performed in the same room two experiments on a dog at different times: one in the morning and one during the afternoon. In the morning all the stimuli, without exception, were reinforced with food, while in the afternoon experiments one of these stimuli was not reinforced. This eventually led to a situation in which the stimulus that was not reinforced assumed a dual signal significance; namely, in the

morning experiments it had the significance of a conditioned positive food stimulus, and in the afternoon experiments that of a conditioned inhibitory food signal. Further experiments showed that even when the problem was made much more difficult, some dogs achieved a solution that was less distinct but still quite clear. In the morning experiments, the experimenter combined a loud sound of a horn with food and produced a corresponding conditioned reflex; at the same time, a soft sound of the horn was differentiated by non-reinforcement. In the afternoon experiments, the same experimenter did just the opposite: the soft sound was reinforced with food and the loud sound was not reinforced. This experimental design disrupted the conditioned reflex activity of several dogs who were unable to solve the problem. However, another group of dogs solved it, although with great difficulty and in a form that was not entirely clear and distinct. In the morning experiments, the loud sound evoked in these animals an excellent alimentary conditioned reflex, and the soft sound sometimes elicited a weak conditioned food reflex or, sometimes, elicited none at all. In the afternoon experiments the opposite occurred: the soft sound evoked a strong conditioned food reflex, and the loud sound produced it in a weak form, or did not produce it at all.

It seems to us that the results of these experiments also speak in favor of the view that chronic conditioned inhibition is localized right in the structures of the conditioned connection. If it were localized in the cortical focus of the conditioned stimulus, the stimuli of the conditioned reflexes inhibited in some experiments should not produce a reflex in the other experiments. Furthermore, if this inhibition were localized in the cortical focus of the unconditioned stimulus, in experiments of the second type the situation would not occur in which one stimulus produced a conditioned reflex and another similar stimulus did not produce it.

The material I have set forth above, concerning the localization of conditioned inhibition in elements of the conditioned reflex arc, has been obtained by us over many years of experiments in the study of trans-switching in conditioned reflex activity, together with other data I shall not describe here since they are not organically related to the question that is the subject of the present report. Referring those interested in our data on the problem of trans-switching in conditioned reflex activity to the papers that have been published by my colleagues and myself, I shall here restrict myself to further mention of the fact that the characteristic feature of these trans-switching experiments is that the same stimulus is simultaneously given two signal meanings (signals of conditioned reflexes of different types, different signs, different delays, or different intensities) each of which is manifested separately, at a different time, under its own conditions, and in its own adequate situation.

Currently we have available entirely new, fresh, factual material on the localization of conditioned inhibition, obtained in experiments of a different sort: namely, when the same stimulus assumes simultaneously the signal values of two conditioned reflexes of different types, alimentary and electrodefensive. Such experiments differ from those of trans-switching in that in their case both meanings of the conditioned stimulus are displayed in parallel, simultaneously, under the same conditions, and in the same situation. This is accomplished by combining the same indifferent stimulus with food in some trials

and with electrical stimulation of one of the animal's paws in other trials, or by reinforcing the stimulus with food and shock simultaneously. The application of the conditioned stimulus thus evokes simultaneously both the conditioned food reflex and the conditioned electrodefensive reflex. FIGURE 4 shows part of a kymograph record of such experiments conducted by my colleague, F. K. Daurova. Moreover it has been found possible to preserve the ordinary unitary (one-UR) conditioned reflexes to the other stimuli in the same animals, together with the new binary conditioned reflexes.

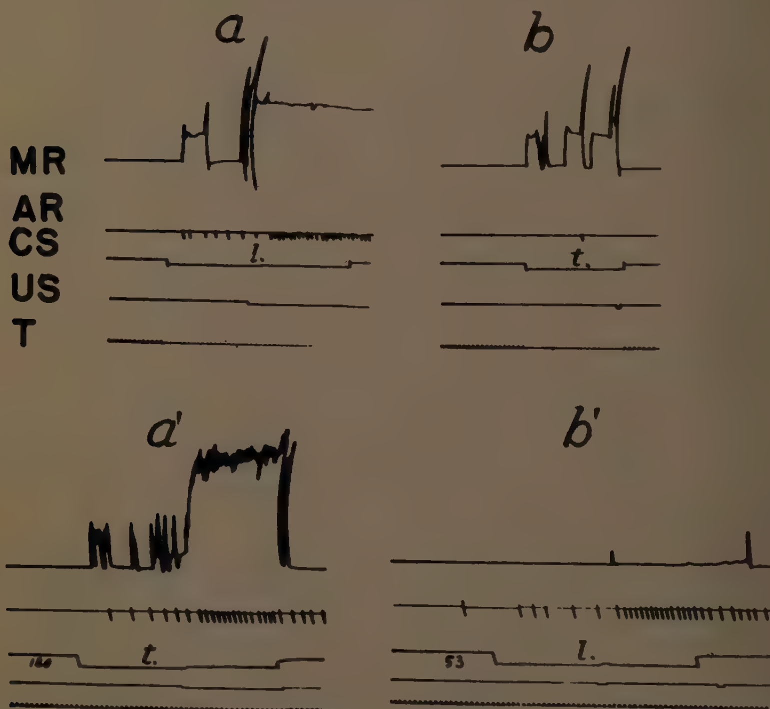

FIGURE 4. Binary (a and a') and single (b and b') conditioned reflexes. Key: MR, motor reflexes; AR, alimentary reflexes; CS, conditioned stimuli; US, unconditioned stimuli; T, time in seconds; l, light stimulus; t, tone stimulus.

Setting aside all the material obtained in our laboratory respecting these binary or dual conditioned reflexes, I shall confine my attention here to a brief description of only those facts that are directly related to the question of the initiation and localization of conditioned inhibition in the elements of the conditioned reflex arc. Daurova, experimenting with the extinction of binary conditioned reflexes by repeated applications of the conditioned stimulus, without reinforcing it with either food or electrical current, found that it was possible to inhibit completely one of the binary conditioned reflexes, specifically the alimentary one, while retaining for a long time the second one: that is, the electrodefensive conditioned reflex (FIGURE 5). It was shown by Daurova that when the stimulus is not reinforced both by electrical current and by food,

the extinction of both conditioned reflexes does not develop in parallel; one reflex is inhibited while the second is still present (FIGURE 6).

It will be noted that in these experiments, in contrast to experiments with trans-switching, the conditioned stimulus elicits both reflexes at the same time within a single experiment under the same conditions. The chronic inhibition of a single reflex that is seen in the case of trans-switching is not developed;

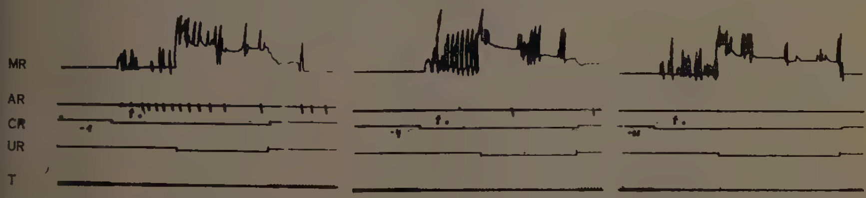

FIGURE 5. Extinction of one of the binary conditioned reflexes. Key: MR, motor reflexes; AR, alimentary reflexes; CR, conditioned response; UR, unconditioned response; T, time in seconds; *t*, tone stimulus.

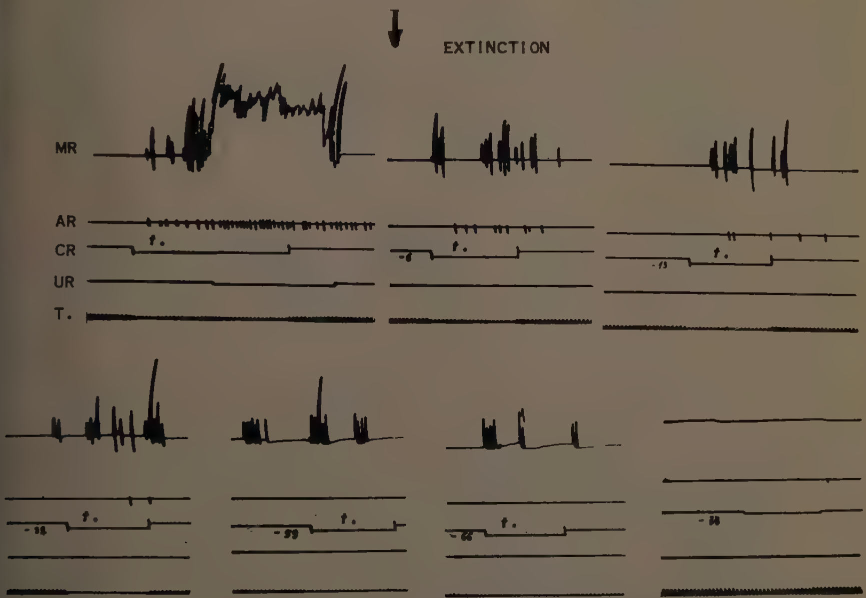

FIGURE 6. Extinction of both binary conditioned reflexes. See the legend to FIGURE 5 for the key to abbreviations.

instead acute inhibition is induced in the course of a single experimental session. The data obtained in these experiments, therefore, seem to be particularly illustrative and persuasive proof of the proposition that conditioned inhibition is initiated not in the focus of the conditioned stimulus but in the connecting elements of the conditioned reflex arc that follow.

In view of the fact that after extinction of the single conditioned reflexes, there remained within the binary conditioned framework single conditioned reflexes to other stimuli that revealed no substantial changes (FIGURE 7), we

may conclude further that this inhibition is not initiated in the focus of the unconditioned stimulus. Again there is no alternative but to admit that conditioned inhibition is initiated and is localized in the elements of the conditioned connection itself.

Certain factual materials on the question of localization of conditioned inhibition have also been obtained in investigations carried out by us in recent years on the problem of bilateral conditioned connections. I should like to supplement what I have said above by citing these data and, in order that the data may be more readily understood, I shall preface my description by noting that in general in our conditioned reflex experiments we usually combine two stimuli, each of which evokes an unconditioned reflex that can be objectively and accurately determined and graphically recorded. Examples of such stimuli are: food; electrical stimulation of the paw; local cooling of a certain region of the skin (in order to elicit a local vasomotor reflex); blowing of air into the

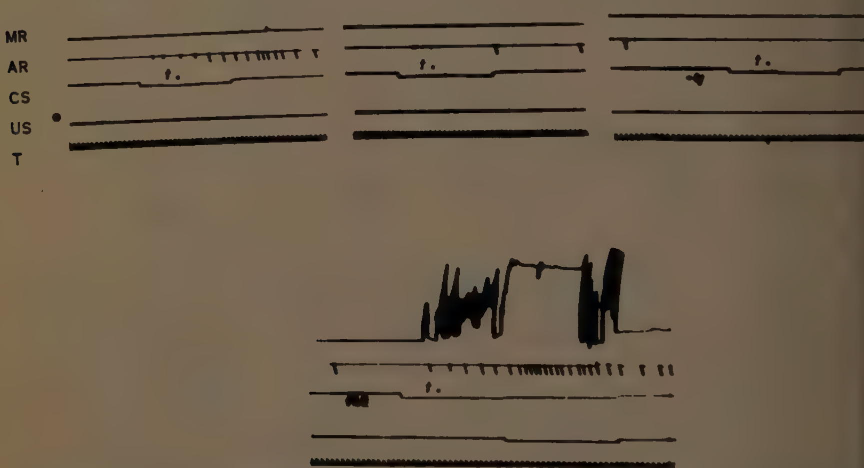

FIGURE 7. Binary conditioned reflex after extinction of the single one. See the legend to FIGURE 4 for the key to abbreviations.

eye (to elicit the eyelid closure reflex); and passive lifting of the paw. (This action was performed to elicit reflex relaxation of extensor muscles, as determined by recording resulting electromyograms; subsequently, as conditioned reflexes are developed, passive movements of the paw become active.) We combined these stimuli in pairs in different combinations, either in stereotyped or in variable sequence. In this case, as a rule, bilateral conditioned connections are developed: each of the two stimuli combined eventually acquires the capacity to elicit, together with its own unconditioned reflex, the reflex of the "partner" stimulus as a conditioned reflex. FIGURE 8 shows schematically the arc of such a conditioned reflex, and FIGURE 9 illustrates the direct and reverse conditioned reflexes elaborated by combination of the eyelid reflex with the passive lifting of a leg. Omitting a detailed characterization of these reflexes and the factual material we have available, I shall cite here only the data that pertain to the localization of conditioned inhibition in the reflex arc of these reflexes.

My colleagues M. Ye. Varga and Ya. M. Pressman[26] produced bilateral conditioned reflexes in dogs by combining, in stereotypical sequence, the stimuli of blowing into the eye and the passive lifting of one paw. When a bilateral reflex (or a reflex with a bilateral connection) had been produced, they extinguished one of the reflexes and thus were able to follow the development of conditioned inhibition in the elements of the conditioned reflex arc through objective events

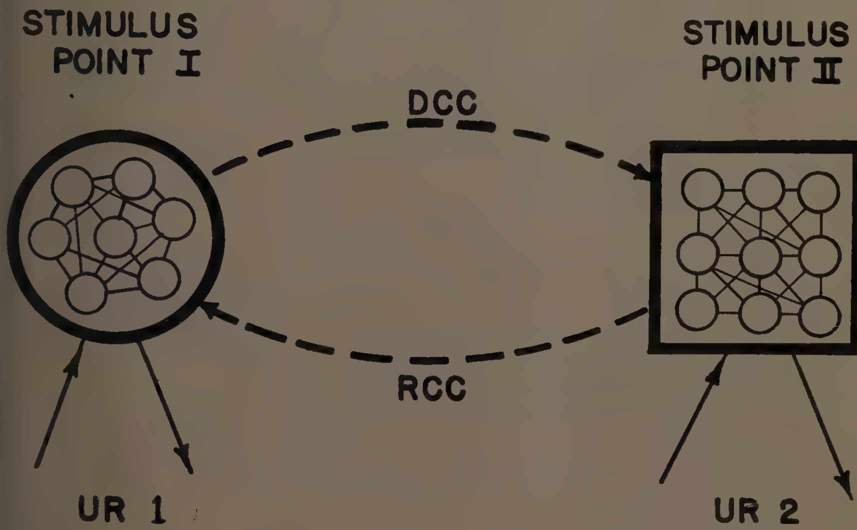

FIGURE 8. Scheme of the conditioned reflex with bidirectional connection. Key: DDC, direct conditioned connection; RCC, reverse conditioned connection; UR 1, unconditioned reflex No. 1; UR 2, unconditioned reflex No. 2.

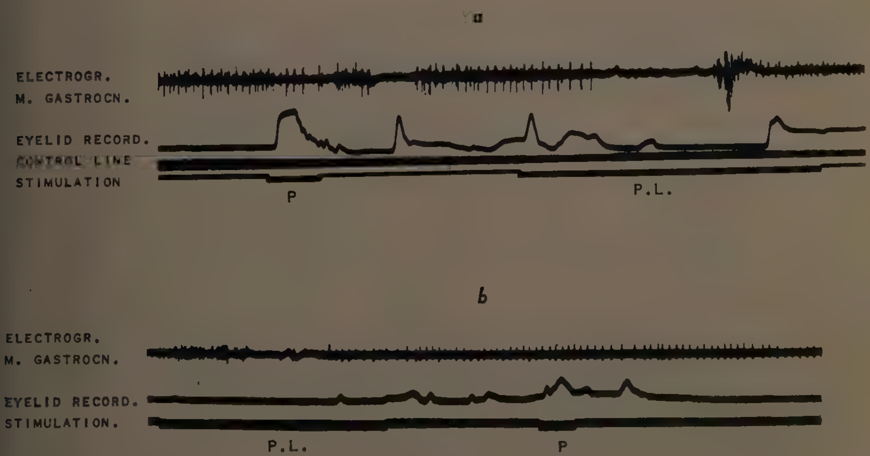

FIGURE 9. Bidirectional conditioned connections between passive lifting of the leg and eyelid reflexes: (*a*) the direct and reverse conditioned connections upon formation of the motor conditioned reflex on puffing air into the eye; (*b*) the direct and reverse conditioned connections upon formation of eyelid conditioned reflex on passive lifting of the leg. P = air puff; P. L. = passive lifting of the leg.

in the foci of the two combined stimuli. The results were interesting. When blowing into the eye was applied without being reinforced by passive lifting of the paw, a wave-shaped extinction of the conditioned paw-lifting reflex occurred at first; later, blowing into the eye not only stopped eliciting flexion of the paw but even began to evoke an antagonistic movement: extension of the paw. The unconditioned reflex produced by blowing into the eye (that is, the eyelid closure reflex) was not weakened, however; on the contrary, it was strengthened, thus showing that its cortical focus not only was liberated from the conditioned inhibition but became even more excitable. Moreover, any assumption that the extinction of the conditioned motor reflex stemmed from the development of inhibition in the cortical focus of the motor reflex to the extremity is not true. For when blowing into the eye no longer produced conditioned lifting of the paw—that is, after complete extinction of this conditioned reflex—passive lifting of the paw evoked conditioned eyelid closure, often in an even stronger form than at the beginning of the experiment (FIGURE 10). Precisely the same results were obtained when the other member of the bilateral reflex was extinguished: that is, when passive lifting of the paw was repeatedly not reinforced by blowing into the eye. In such experiments, the wave-shaped course of extinction of the conditioned eyelid reflex finally led to a situation in which lifting of the paw not only ceased to elicit the conditioned eyelid closure reflex but even produced the antagonistic effect: strong and prolonged opening of the eyelids. Again, after the onset of the extinction of the conditioned eyelid reflex, blowing into the eye evoked conditioned lifting of the paw, often in a more intense form than at the beginning of the experiment.

Similar data obtained by M. I. Struchkov[27] with other bilateral reflexes have been produced by combining food either with passive lifting of one paw or with local cooling of a restricted portion of the skin on the test animal's side. In the first variation, giving food elicited conditioned reflex lifting of the paw, and passive lifting of the paw elicited a conditioned food reflex. In the second variation, giving food evoked a local skin vasomotor conditioned reflex, and cooling of the skin evoked a conditioned alimentary reaction (FIGURE 11). When Struchkov carried out extinction of one of the bilateral conditioned reflexes, specifically when he gave food repeatedly without reinforcing it by lifting the paw, the giving of food continued to elicit an alimentary reaction after complete inhibition of the conditioned paw-lifting reflex previously evoked by it; in addition, passive lifting of the paw during this period elicited a conditioned food reflex. In the main, the same results have been obtained also with extinction of the vasomotor conditioned reflex to the giving of food.

The results of these experiments by Struchkov, as well as those of Varga and Pressman's experiments, indicate—with greater clarity and persuasiveness than the findings of our other colleagues, which we described earlier—that conditioned inhibition is initiated and is initially localized precisely in the structures of the conditioned connection itself, and definitely not in the cortical foci of the conditioned and unconditioned stimuli.

As I said at the beginning of this paper, I grant that when conditioned inhibition subsequently becomes more profound in the structures where it is initiated, it can then spread both to the focus of the conditioned stimulus and to the focus

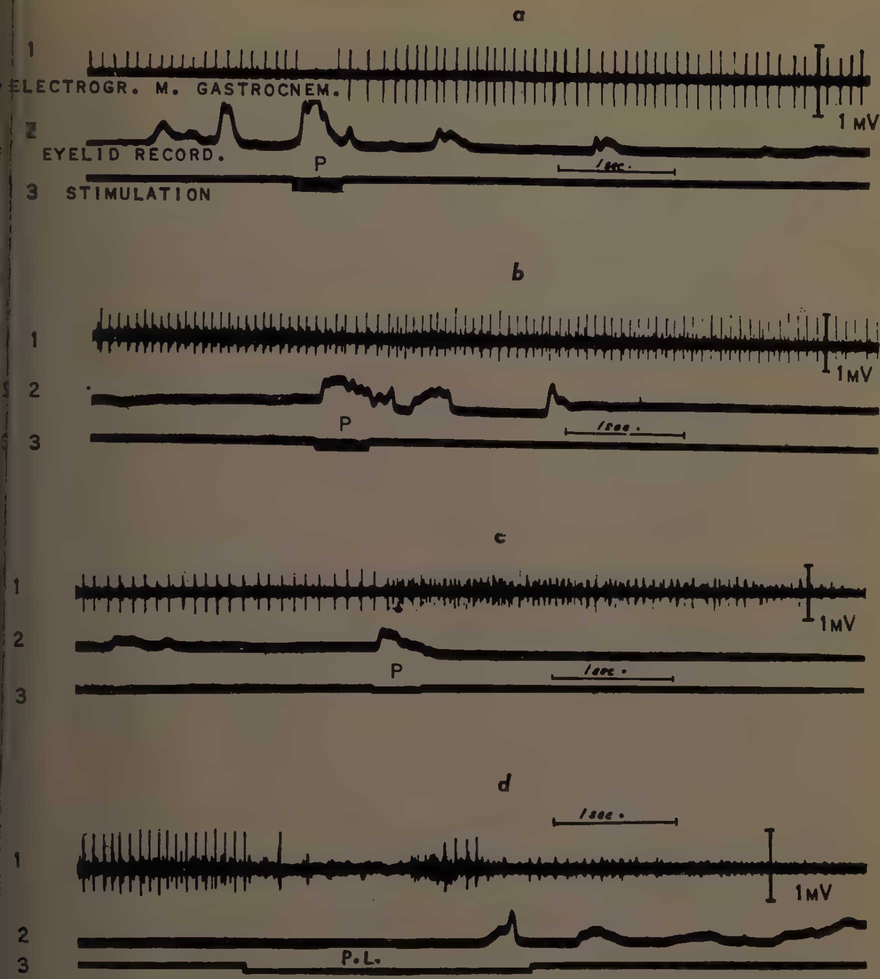

FIGURE 10. The eyelid conditioned reflex (*d*) to the passive lifting of the leg after extinction of the motor conditioned reflex of the leg to the stimulus of blowing air into the eye (*a*, *b*, and *c*). P = air puff; P. L. = passive lifting of the leg.

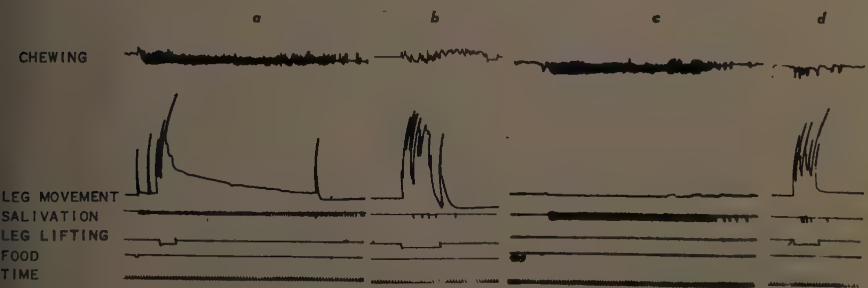

FIGURE 11. The bilateral motor-defensive and alimentary conditioned reflexes, shown in *a* and *b*. The maintenance of the alimentary reflex to the electrical stimulation of the leg (*d*) is shown after extinction of the motor-defensive reflex to the food (*c*). Key: *a*, the direct conditioned connection; *b*, the reverse conditioned connection; *c*, the extinguished direct connection; and *d*, the test of reverse connection after the direct one is extinguished.

of the unconditioned stimulus (that is, it can encompass to some degree all central components of the conditioned reflex arc). This is manifested by weakening of the unconditioned reflex, by weakening of the original reaction to the conditioned stimulus, and by development of a state of drowsiness and sleep. However, as is clear from all that I have said above, these phenomena, long known from the great wealth of material from the Pavlovian laboratories, are treated somewhat differently by us than by the previously mentioned investigators. Those who hold the view that conditioned inhibition is initiated in the focus of the conditioned stimulus or in the focus of the unconditioned stimulus regard the phenomena of the spread of inhibition as the result of subsequent deepening of the initial inhibition in the foci of the conditioned or the unconditioned stimuli. Unlike them, we suggest that conditioned inhibition is initiated in the structures of the conditioned *connections*, and that as inhibition subsequently deepens in these structures it spreads to the foci of the conditioned and unconditioned stimuli and, in general, to other central nervous structures. The possibility has not been ruled out, of course, that in particular conditions of an extraordinary nature inhibition can also be initiated in the foci of the conditioned or unconditioned stimuli and, subsequently becoming more profound in these structures, lead to various consequences. However, our data give us sufficient reason to believe that this usually does not happen: that as a rule conditioned inhibition is initiated in the structures of the conditioned connections and appears and becomes intensified much later than this in the foci of the conditioned or unconditioned stimuli.

In behalf of the viewpoint I am defending I shall cite still other results of new experiments by my colleagues L. I. Chilingaryan and Ye. A. Romanovskaya,[28] and with this conclude my presentation of the factual data obtained in our laboratory up to the present time on the problem of initiation and the initial localization of conditioned inhibition in elements of the conditioned reflex arc.

These experiments are performed on dogs with previously inserted contact electrodes to the cortical motor points of one of the paws, which makes it possible, under chronic experimental conditions, to produce movements of that paw by electrical stimulation of the corresponding cortical points, and to trace changes in the level of excitability of these points under the influence of various agents and factors. In such dogs Chilingaryan developed motor conditioned reflexes by combining an indifferent sound with electrical stimulation of corresponding points in the motor cortex. Romanovskaya, on the other hand, produced conditioned motor reflexes in such dogs by different means: by combining an indifferent stimulus with electrical stimulation of the paw. When conditioned reflexes had been developed and had reached a certain level of stability, the experimenters produced extinction of these conditioned reflexes while they followed directly the dynamics of the changes in the excitability of the corresponding cortical points (in comparison with the original level) by means of direct measurements. They obtained the following similar data. In the course of the wave-shaped extinction of the conditioned reflex, the excitability of the cortical motor points was initially somewhat elevated, then returned to its initial level; later, as the degree of conditioned inhibition became deeper, a rapidly progressing fall in cortical excitability ensued, leading finally to a sharp and prolonged drop in the excitability of this point below the original

level. Sometimes the threshold value of the stimulating current was increased three to four times, and even more, above the initial value. For comparison, I might point out that in the usual control experiments carried out by these colleagues, in which extinction of conditioned reflexes was not produced, a shift of the opposite character (that is, a gradual and steady elevation of excitability of the cortical motor point for the paw) occurred as a rule in the course of the experiment in complete agreement with the data of many other investigators.

Although these experiments by Chilingaryan and Romanovskaya are to a certain extent of a preliminary character, and although the data obtained in these experiments require further and more detailed investigation, nevertheless the reliability of the facts themselves is beyond all question since they have been checked in a large number of experiments on seven dogs of different types and ages.

Thus the data obtained in these experiments by direct recording, concerning the absence of substantial changes in excitability of the cortical focus of the unconditioned motor reflex at the stage of shallow extinction, and the significant reduction in its excitability at the stage of profound extinction, are in complete agreement with our other data described above. They indicate, specifically, that conditioned inhibition is not initiated in the cortical focus of the unconditioned reflex, but appears there later after a marked deepening of inhibition.

At the present time we have at hand some factual data pertaining to the initiation and localization of another type of cortical inhibition: namely, transmarginal inhibition. These data, obtained by our co-worker F. K. Daurova,[29] may be summarized as follows. In a series of experiments on trans-switching, a conditioned food reflex was developed in dogs to a tone at a frequency of 1100 cps and 45 db. intensity in one experimental situation, and an electrodefensive conditioned reflex was developed to the same stimulus in another situation. Both experiments were conducted on the same day, in no particular order. When both conditioned reflexes had reached a certain degree of stability and clarity of trans-switching, Daurova performed experiments on transmarginal inhibition by increasing the intensity of the conditioned stimulus to 105 to 115 db. without reinforcement in both experimental situations. The results proved highly interesting. When the intensity of the conditioned stimulus was greatly increased in this fashion, the stimulus stopped eliciting the conditioned food reflex but continued to elicit the conditioned defensive reflex; in other words, it became transmarginally inhibitory for one activity, while at the same time it retained its positive signal significance for the other activity (FIGURE 12).

Essentially analogous results were obtained by Daurova in a second series of experiments on binary conditioned reflexes, in which she experimentally developed both alimentary and electrodefensive conditioned reflexes to the same sound at 45 db. intensity in the same situation and in the same experiments. When the two conditioned reflexes reached a certain stability and the conditioned stimulus elicited simultaneously both conditioned reflexes in a rather strong form, experiments were carried out on the demonstration of transmarginal inhibition by means of a sharp extraneous intensification of the conditioned stimulus. These results proved to be the same as those in the previous series of experiments: that is, the conditioned food reflex disappeared but the

electrodefensive conditioned reflex remained (FIGURE 13). On the other hand in another experiment on trans-switching and binary conditioned reflexes Daurova increased the amount of food reinforcement for the tone of 45 db

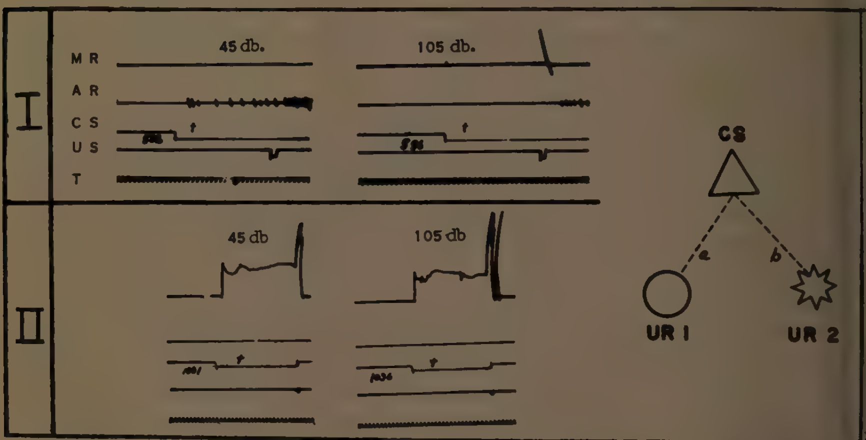

FIGURE 12. Supermaximal inhibition on switching of conditioned reflexes. Key: I, alimentary circumstances; II, defensive circumstances; MR, motor reflexes; AR, alimentary reflexes; CS, conditioned stimuli; US, unconditioned stimuli; T, time in seconds; UR 1, unconditioned reflex No. 1; UR 2, unconditioned reflex No. 2; *t*, tone stimulus.

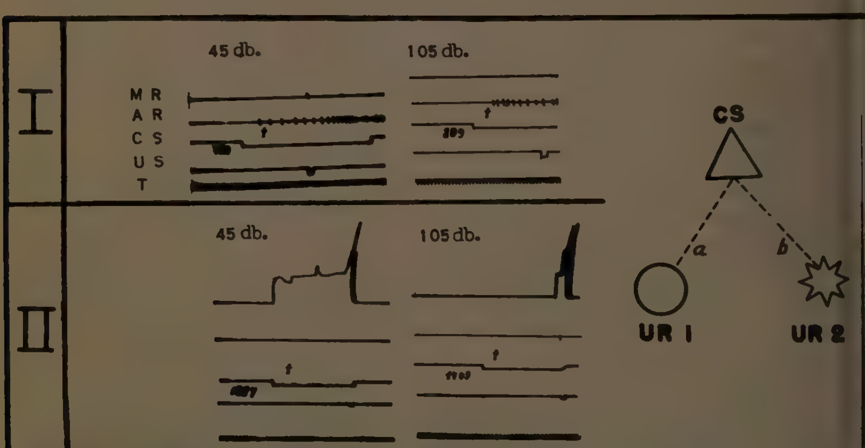

FIGURE 13. Supermaximal inhibition on switching of conditioned alimentary (strong and defensive (weak) reflexes. See the legend to FIGURE 12 for the key to abbreviations. In this experiment the food portion is doubled and the electrical stimulation is weakened.

(70 gm. of meat-biscuit powder, instead of 30 gm. as in the previous experiments) and greatly reduced the electric current. When the conditioned reflexes had been developed she conducted experiments along the lines of the experiments described above to demonstrate transmarginal inhibition by a sharp extraneous intensification of the tone. This time, however, the electro-

defensive conditioned reflexes were found to be inhibited, and the food reflexes were retained.

Daurova also obtained some data on supermaximal inhibition in the experiments with binary conditioned reflexes. When, during this experiment, she intensified the strength of the stimulus from 45 to 105 db., the supermaximal inhibition did not develop simultaneously in both reflexes; one of them was inhibited, while the second one still persisted (FIGURE 14).

The general conclusion from all these experiments is clear. Since, in response to the application of an extremely intense conditioned stimulus, only one of the two conditioned reflexes normally elicited by that stimulus is inhibited, it is evident that the transmarginal inhibition that arises is localized not in the cortical focus of the conditioned stimulus, as Pavlov assumed and as is commonly supposed, but in the components of the conditioned reflex arc that follow it. The question of precisely what components are involved is currently being studied by Daurova.

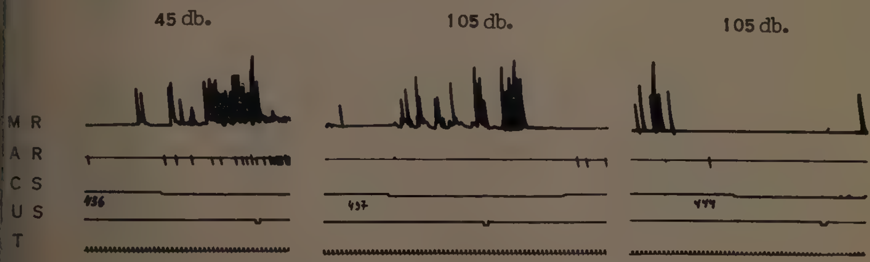

FIGURE 14. Supermaximal inhibition with binary conditioned reflexes. See legend to FIGURE 4 for the key to abbreviations.

This completes the exposition of the principal data from our laboratory concerning the problem of the initiation and localization of cortical inhibition in the elements of the conditioned reflex arc. We are presently conducting investigations in this area and expect to continue them in the future; for this purpose we are beginning to use methods for recording the electrical activity of the cortex in our experiments. To what final conclusion the results of our new experiments will lead is difficult to predict. However the data available at present permit us to believe that conditioned inhibition is initiated and is initially localized in the elements of the conditioned connection, not in the focus of the conditioned stimulus or in the focus of the unconditioned stimulus, as other investigators believe. According to the same data, transmarginal inhibition is initiated and is initially localized not in the cortical focus of the conditioned stimulus, as is commonly believed at present, but in subsequent components of the conditioned reflex arc. With respect to the initiation and localization of external or unconditioned inhibition, we still do not have reliable data at hand.

In conclusion I shall make the following observation. So as not to complicate a task as difficult as this one, I have deliberately not concerned myself in this paper with the problem of the mechanism of inhibition, with its nature,

or with other aspects of the problem of inhibition. I should observe, however, that in our opinion the viewpoint of the investigator concerning the mechanism of development or the nature of inhibition is not of crucial importance for the essence of the question here under discussion.

In this paper I have constantly spoken of the initiation and localization of cortical inhibition. This is because my colleagues and I hold the view that, at least in higher animals and man, the conditioned reflex is closed between two cortical points and the conditioned connection passes through cortical structures. It is well known that at the present time the question of the closure of the conditioned connection in the higher divisions of the central nervous system—by which I mean the question of the localization of the central portion of the conditioned reflex arc—is the subject of intensive discussion. We have not been concerned, deliberately, with the existing points of view on this question, for the same reasons that motivated us to avoid discussing the nature and mechanism of initiation of inhibition in the cerebral structures. What views an investigator holds on the question of the localization of the conditioned connection in cerebral structures is similarly not of essential importance to the question under discussion.

In conclusion, I note my own great satisfaction with the fact that the results of the investigations that my colleagues and I carried out have permitted us to some extent to develop further, and at a number of substantial points to make more precise and to supplement, the ideas of our great teacher Pavlov on the problem of inhibition: one of the most complex and important problems of higher nervous activity.

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AN EXPLORATION OF THE FUNCTIONAL RELATIONSHIP BETWEEN ELECTROENCEPHALOGRAPHIC POTENTIALS AND DIFFERENTIAL INHIBITION*

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In numerous studies which have been reviewed elsewhere,[11] a set of marked and relatively consistent changes in the electrical activity of the brain has been observed to occur during elaboration of a conditioned response (CR). The experiments we shall describe here were an attempt to evaluate the validity of interpreting such macropotential configurations as a manifestation of neural mechanisms related to the coding, transmission, and processing of information involved in the generation of the conditioned response. The electrographic data that led to our studies were primarily derived from researches in which intermittent stimuli were used as the conditioned stimuli (CS). A number of workers have observed that potentials at the same frequency as the CS appear in a variety of brain structures during conditioning, and alter their configuration during the elaboration of a CR. Such frequency-specific potentials have been observed in different species of animals and in a variety of behavioral training situations.

In addition to changes in the spatial distribution of frequency-specific responses to an intermittent CS during elaboration of a CR, Livanov and Poliakov[16] originally noted a phenomenon they referred to as "assimilation of the rhythm." By this they meant that the frequency-specific potentials that come to characterize the response to the CS at a number of brain sites also begin to appear spontaneously in the interval between presentations of the CS. This internalization or assimilation of the rhythm suggests that the brain may have the capacity to represent the temporal characteristics of a stimulus in its absence. Numerous confirmations of this phenomenon have been reported in a wide variety of experimental animals.[11]

Further evidence of the capacity of the central nervous system to generate a "representation" of a previously experienced temporal sequence of stimulation has been provided by John and Killam.[12] These workers noted that after a cat had been trained to perform a response to a light flickering at frequency F_1, presentation of a new flicker frequency F_2 resulted in generalization; that is, the previously established CR was performed to the new stimulus. During such generalization electrical activity in certain regions of the brain occurred at a frequency corresponding to that of the CS used during training, rather than to the frequency of the new stimulus that was actually presented.

Basically similar data have been presented by Majkowski.[18] After elaboration of a conditioned response to light flickering at a particular frequency, he observed frequency-specific potentials on the motor cortex in response to the CS. When a flicker frequency different from the training frequency was introduced, potentials at the frequency of the presented light appeared on the

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visual cortex, whereas on the motor cortex hypersynchronous waves appeared at the frequency used throughout training. Majkowski suggested that the new signal somehow made connection with a system previously elaborated to the old stimulus, reflecting its temporal characteristics. Furthermore, the observation reported elsewhere in these pages by Jasper and Majkowski of phasic movements at the same frequency as the macropotentials observed in the nervous system, appearing in the conditioned motor response of an animal trained to a rhythmic CS, suggests some functional relevance to these frequency-specific neural events.

These various studies seem to indicate that the spatial and temporal pattern of neural activity that becomes evident as a consequence of the experience of the animal possibly may be causally implicated in the elaboration and performance of conditioned behavior under these circumstances. What may be a crucial insight into a mechanism that might provide the means for storage of such temporal sequences of stimulation is found in the work of Morrell, described by him in this monograph. He has clearly shown that during anodal polarization of the visual cortex a neural unit discharges at a rate stipulated by the frequency of a flickering light. Subsequent to the cessation of anodal polarization, the presentation of a single flash of light triggers unit discharges at the same frequency as the previously experienced flicker. This observation is clearly relevant to the previously described phenomenon of assimilation.

A question arises from these phenomena described by Morrell: What is the origin of the frequency-specific discharge of these units observed in response to a single flash following cessation of anodal polarization? Does the responsible mechanism reside in the unit itself? Or did polarization enhance the cortical influence of an assimilated rhythm persisting in nonspecific structures of the nervous system, as reported by Yoshii *et al.*?[24]

What might be the functional significance of these phenomena? A mechanism of this sort would appear to provide means for storage of a representation of a temporal sequence of events, lasting beyond the duration of the events themselves.

Such a mechanism for internal representation of a past event seems, on logical bases, to be essential to enable an animal to perform two differentiated responses to two similar stimuli, either of which may be presented in a given experimental situation. This is particularly true if the two conditioned stimuli are, for example, two frequencies of flickering light, which cannot be discriminated on the basis of the characteristics of a single constituent flash. To account for differential performance in response to two such similar stimuli differing only with respect to their temporal sequence, we must invoke some facility for storage of a representation of the temporal sequence of previously experienced events in order to permit comparison with a present input, thus making identification possible.

As has been evident from other statements in this monograph, Sokolov has also recognized, on both logical and experimental bases, the need for such a comparator; he proposes the cortex as its location. Pribram has also pointed out the need for a comparator. John and Killam[13] have presented evidence suggesting that, if one considers macropotentials to be related to the coding of information, a comparator function might be inferred to exist between the so-

called nonspecific areas of the brain and the specific sensory system. Our data suggest that the internalized representation of prior experience may be in the nonspecific system where assimilated rhythms arise earliest, and that a comparison between events in this core system and events in the specific sensory systems, reflecting present input, determines the behavioral outcome on any particular trial.

These various considerations led our group to investigate further the question of whether these frequency-specific potentials might be information. When animals are trained to perform a differential discrimination between two flicker stimuli differing in frequency, are the observed frequency-specific potentials a reflection of the coding and processing of information causally related to the behavioral performance, or do they merely reflect generalized processes of excitation and inhibition that are not specifically informational, and that bear only a relationship of concomitance with the behavioral performance?

The data gathered thus far in our attempt to analyze the coding function of macropotentials have forced upon us the consideration of a related but quite unforeseen question, that of the role played by slow waves in processes of internal inhibition. In our choice of stimulus frequencies and in our choice of a differentiated avoidance response, we had unwittingly set the stage for the powerful intrusion of processes of internal inhibition. As a result the generality of our findings with respect to coding must be somewhat restricted, while unexpected observations on the role of slow inhibitory processes have provided some insights into processes of internal inhibition.

In various studies of the electrographic characteristics of the process of differentiation, a set of apparently contradictory phenomena have been reported. On the one hand, there have been a number of reports that differentiation is characterized by the appearance of slow hypersynchronous electrical activity[9,19,17,8,23,10] in response to the negative or inhibitory CS, which has been interpreted by some authors as the manifestation of the inhibitory process itself.

On the other hand, reports of sustained desynchronization and increased amplitude of evoked potential responses to the conditioned and differential stimuli also exist.[5,2,22,15,24] These two sets of findings might be reconciled with each other if the desynchrony were due to the consequences of unexpected nonreinforcement, if the increased amplitude of evoked potential responses were related to the necessity to represent stimulus attributes in sufficient detail to permit differential rather than existential identification, and if the hypersynchrony were related to the inhibitory process itself. Which aspect of these phenomena was salient in the data might depend on a number of features of the particular experimental situation and the particular stage of differentiation during which electrographic data were gathered. Some of our findings seem relevant to these questions and to the question of possible localization of these processes anatomically.

Procedures

Surgical procedure. The data to be described have been gathered from two cats. In both of these cats, six cortical and 11 subcortical electrodes were chronically implanted into the same set of locations, using stereotaxic technique.

Since these animals are currently in active experimental use, no histological verification of placements is yet available. The intended electrode placements were visual cortex, auditory cortex, medial suprasylvian cortex, dorsal hippocampus, ventral hippocampus, mesencephalic reticular formation, centralis lateralis, centre median, medialis dorsalis, and the lateral geniculate body. The lateral geniculate electrode was implanted unilaterally; all other placements were made bilaterally into symmetrically located points. A four-electrode bilateral array was used for the complex: bilateral centralis lateralis-centre median-medialis dorsalis. Cortical electrodes consisted of silver wires, insulated except for the tip resting on dura. All subcortical electrodes were bipolar 0.010 inch stainless steel electrodes, insulated to the tip and separated by 1 mm. Electrodes were soldered to a Winchester 26 connector subminiature plug, which was cemented to the skull using Nu-Weld dental cement.

Apparatus. All experimental procedures were carried out in a shielded sound-resistant box, 22 inches high × 22 inches wide × 23 inches deep, placed in an electromagnetically shielded sound-resistant cubicle. The interior of the box was painted glossy white. One wall was a window, enabling observation of the animal through a one-way vision screen in the cubicle wall. One 15-watt DC bulb, recessed in the top, provided a low level of constant background illumination. A Grass PS-2 Photo Stimulator mounted in the top provided a source of flickering light for experimental stimuli. A brass grid in the floor of the apparatus enabled electric shock to be delivered to the animals' feet. A microswitch lever protruded from one end of the box, 11 inches above the floor, extending 4 inches into the inside. A pilot light mounted above the lever was actuated by the lever. Microdot wire was used in the cables that connected the animal to the apparatus. These cables then passed through the wall of the cubicle. All recordings were obtained using an Offner Type T electroencephalograph. Grass SD-5 stimulators were used to provide the waveforms for central stimulation.

Training. After a period of 3 to 6 weeks for recovery after surgery, control EEG recordings were obtained of the electrophysiological responses to a number of 15-second-long trains of flickering photic stimulation delivered by the photostimulator lamp above the animal, using intensity 16 on the PS-2. Recordings were made from all structures in both animals, using both a 10-cps and a 4-cps flicker frequency. The cats were then trained to perform a conditioned-avoidance response (CAR) to flickering light, pressing the lever to avoid electric shock to the feet within 15 seconds after the onset of flicker. In cat No. 10, the conditioned stimulus (CS) for the CAR was the 10-cps flicker. In cat No. 4, the CS was the 4-cps flicker. Throughout the training period, each cat experienced only the flicker frequency that had been selected as the positive CS. Twenty trials were conducted in each training session, randomly spaced an average of one minute apart. Cat No. 10 reached the criterion of 95 per cent CAR in 20 sessions; cat No. 4 in 17 sessions. Following achievement of criterion, EEG recordings were again obtained of the response of all structures to the CS frequency and to the other flicker frequency, now presented for the first time since the onset of training.

After these post-CAR recordings had been obtained, differential training was initiated. In each session, 20 presentations of the positive CS (S^D) were

randomly interspersed with 20 presentations of the other flicker frequency (S^{Δ}). Performance of the lever-pressing CAR to the S^{D} was maintained, but lever pressing during presentation of the S^{Δ} was punished by electric shock to the feet. A differential CAR, consisting of lever pressing to the S^{D} but not to the S^{Δ}, was established to the 95 per cent criterion level in 30 sessions by cat No. 10 and in 23 sessions by cat No. 4. In cat No. 10, 10-cps flicker served as the S^{D} and 4-cps flicker served as the S^{Δ}. In cat No. 4, 4-cps flicker was the S^{D} and 10-cps flicker was the S^{Δ}. Following achievement of criterion, EEG recordings were again obtained from all structures in response to both flicker frequencies.

Central stimulation procedure. To investigate the effects of central stimulation of various structures at the two signal frequencies, the following procedure was devised. After pilot experiments showed that low frequency stimulation was ineffective, a standard "carrier" wave form was selected, consisting of a 100-cps biphasic square wave, 2 msec. in pulse duration. By modulating one SD-5 stimulator providing the "carrier" with a second SD-5 stimulator used at the signal frequency, trains of pulses were generated that consisted of bursts of 100-cps biphasic pulses, occurring either four or ten times per second. The test procedure for evaluation of central stimulation effects consisted of presenting flicker at the S^{D} frequency concurrently with central stimulation, using the "carrier" pulsed at the same frequency. The stimulus current was gradually increased until the CAR was no longer elicited in response to concurrent photic and central stimulation. Central stimulus current was monitored by observing the voltage drop across a 1 K* resistor in series with the stimulating electrodes. The current level at which central stimulation at the S^{D} and S^{Δ} frequency blocked performance to concurrent photic stimulation at the S^{D} frequency was defined as the *occlusion threshold*, or cut-off. The current intensity at which CAR reappeared to concurrent photic and central stimulation at one signal frequency *but not the other* was defined as the *differential threshold*. In each cat, the occlusion threshold was determined for each structure. The current values were then decreased until the differential threshold was reached, if such existed. A series of trials was then carried out to determine the reliability of the differential effect. Throughout the stimulation session following determination of the occlusion threshold, trials were presented in the counterbalanced sequence:

Peripheral at frequency A
Peripheral at frequency A + Central at frequency A
Peripheral at frequency A + Central at frequency B
Peripheral at frequency A
Peripheral at frequency A + Central at frequency B
Peripheral at frequency A + Central at frequency A

Current values used were well within the range reported by Delgado[6] to cause no histologically demonstrable signs of damage.

* One thousand ohms.

Results

The primary purpose of these experiments was to investigate mechanisms that mediate the coding and processing of information in differential conditioned-response performance. First, the electrical activity of many regions of the brain was studied as conditioned-avoidance responses were differentially established in two cats to the same two stimuli, with the significance of the stimuli opposite for the two animals. Second, the effects of manipulating certain aspects of the stimuli and of drug administration were explored, to see whether covariation in electrical and behavioral activity might provide insights into the functional significance of certain aspects of the electrical activity evoked by the conditioned stimuli. Third, an attempt was made to evaluate directly the functional significance of frequency-specific activity observed in particular structures in the brain of the fully conditioned cat by studying the behavioral consequences of direct electrical stimulation of regions of the brain while the conditioned stimuli were simultaneously presented. In the course of these studies, a number of observations were made that seem relevant to the problem of mechanisms of differential inhibition. In this section we confine our discussion primarily to cortical electrographic aspects of inhibitory processes.

Figure 1 shows the electrical activity recorded from various brain structures in the two cats in response to the presentation of a 10-cps flicker before avoidance training began.

Figure 2 shows the activity recorded in response to the presentation of a 4-cps flicker before the onset of training.

Figure 3 shows the response of both cats to a 10-cps flicker after avoidance training of Cat 10 with a 10-cps flicker CS and Cat 4 with a 4-cps flicker CS. Note that in both animals the response to the 10-cps flicker is much more marked in several structures. In Cat 10, the response of visual cortex is predominantly at 10 or 20 cps, displaying the multiple frequency response that has been reported elsewhere.[13] However, in Cat 4, although the response of visual cortex is initially at 10 cps, note that it shifts abruptly to a marked slow wave at about 5 cps. Shortly after this shift, a startle response is observed, followed by performance of the CAR, which had been established to a 4-cps flicker in this animal. This performance of a conditioned response to an indifferent 10-cps flicker, accompanied by large slow waves on the cortex, would suggest that the slow hypersynchrony seen here serves an excitatory rather than an inhibitory function.

Figure 4 shows the response of both cats to a 4-cps flicker at the same stage of learning. Note again that the response to this stimulus is now more marked in several structures than it was before training. In Cat 4 the response of the visual cortex is predominantly at 4 or 8 cps. Analogous to the data presented in the previous figure, note that Cat 10 responds to the 4-cps indifferent signal with massive 4-cps slow waves on the visual cortex, and nonetheless performs the CAR that was established using a 10-cps flicker CS. These data also suggest that the slow hypersynchrony seen here serves an excitatory rather than an inhibitory function.

FIGURE 5 shows the response of both cats to the 10-cps flicker at the end of differentiation training. For Cat 10, the 10-cps flicker is the positive stimulus for performance of the CAR to avoid shock. For Cat 4, the 10-cps flicker is an inhibitory stimulus, since a lever-pressing response to that frequency is

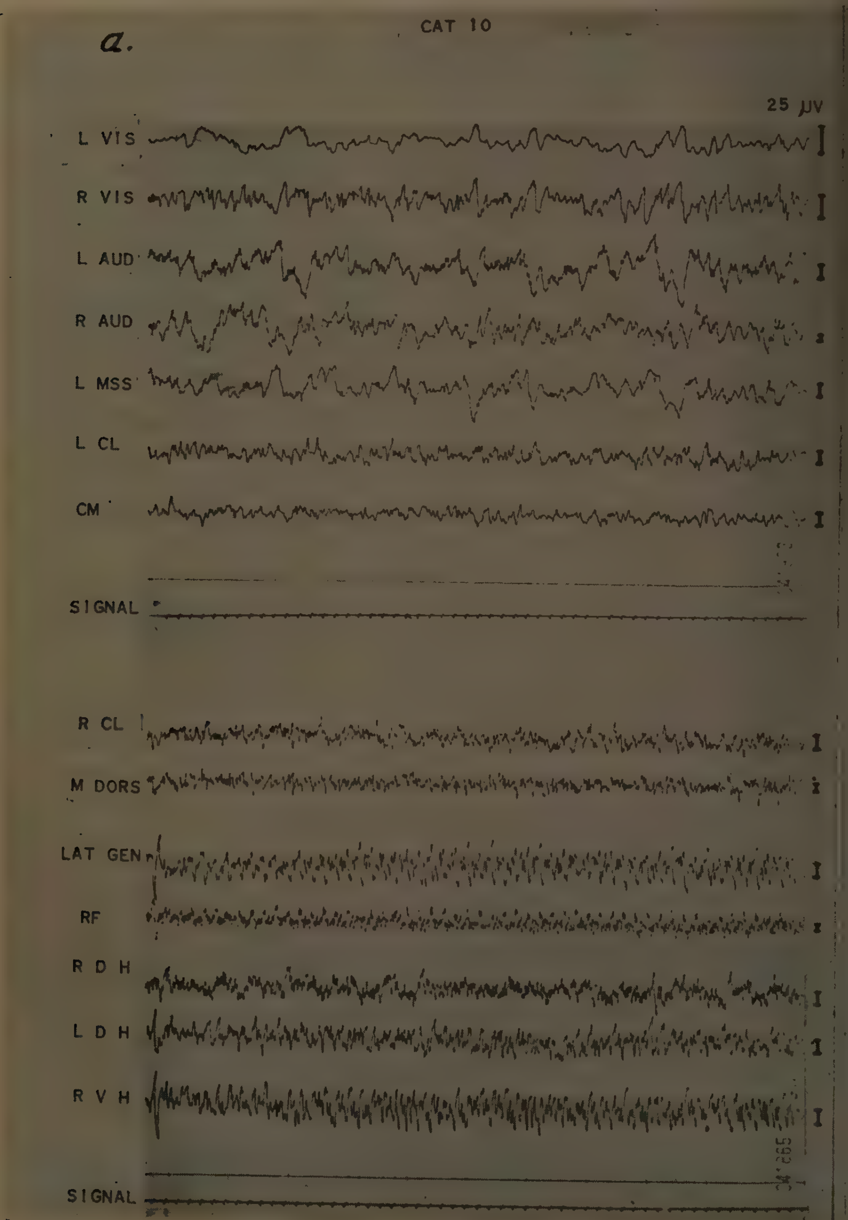
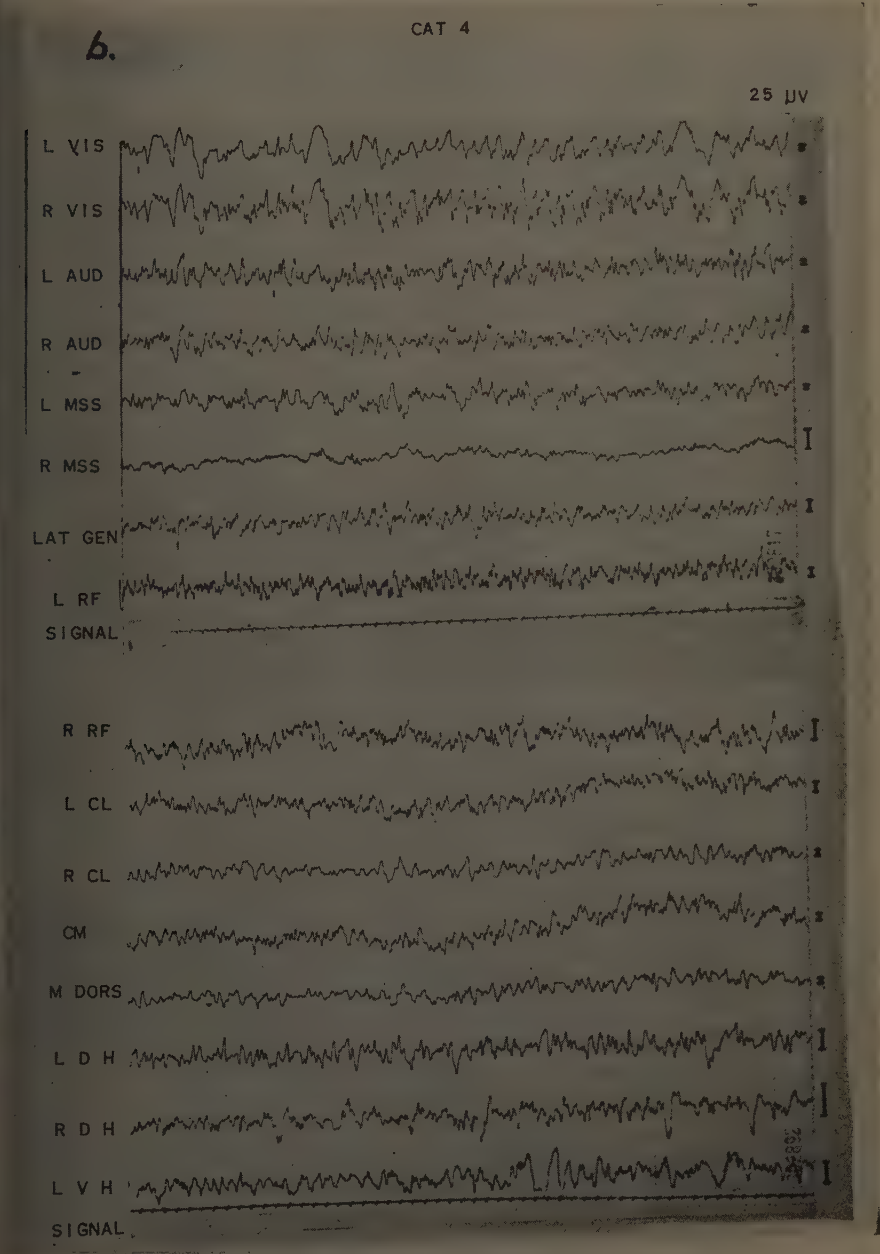


FIGURE 1. Response to 10-cps flicker before

punished by shock. Note that in Cat 10 the response is similar to that seen previously after avoidance conditioning. The lower portion of the recordings from Cat 10 shows a slow 5-cps wave in the visual cortical derivation. This 5-cps activity shifts first to a 10-cps and then to a 20-cps activity before re-



CAR training in Cat 10 (*a*) and Cat 4 (*b*).

sponse occurs. Slow activity, as illustrated here, was characteristically ob- served when the cat performed the CAR with a longer latency than usual. Frequency-specific response appears markedly in a number of structures. In contrast to the earlier picture, the response of Cat 4 is no longer characterized by the faster mode of initial cortical activity, but there is a predominantly 5-cps

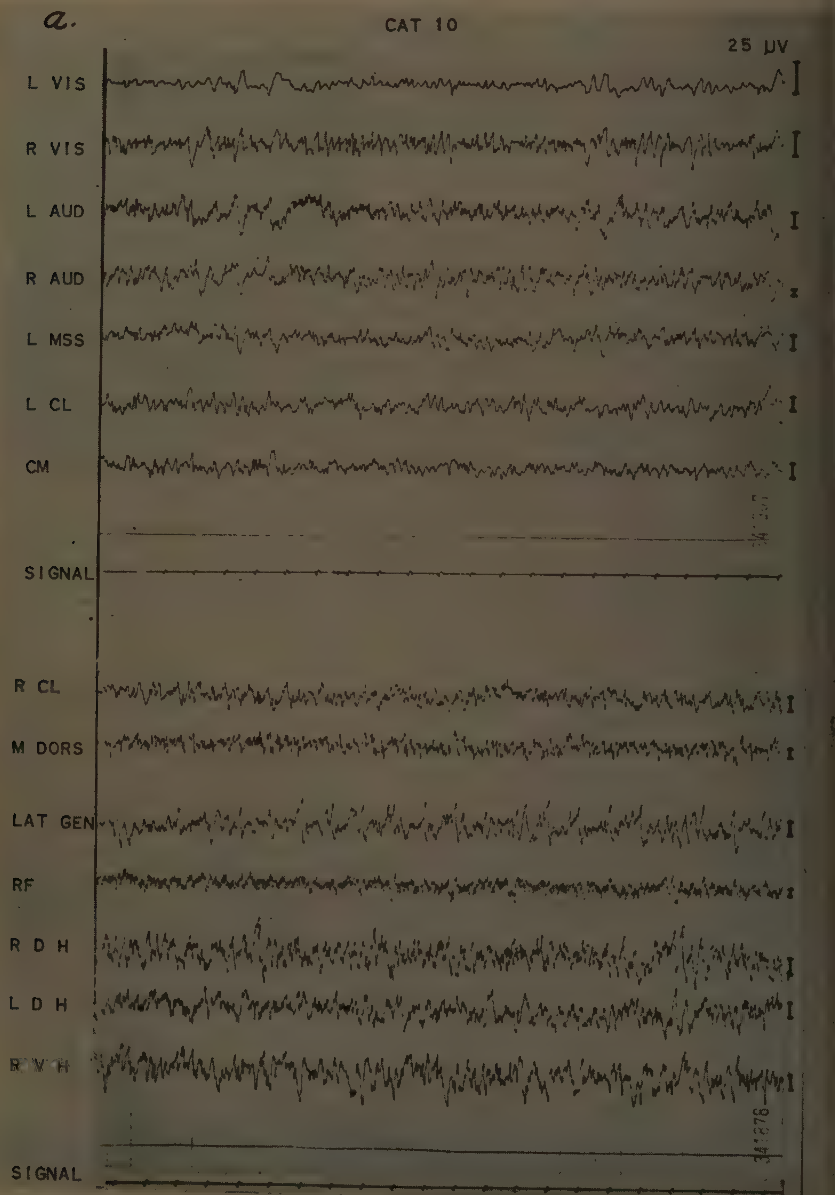
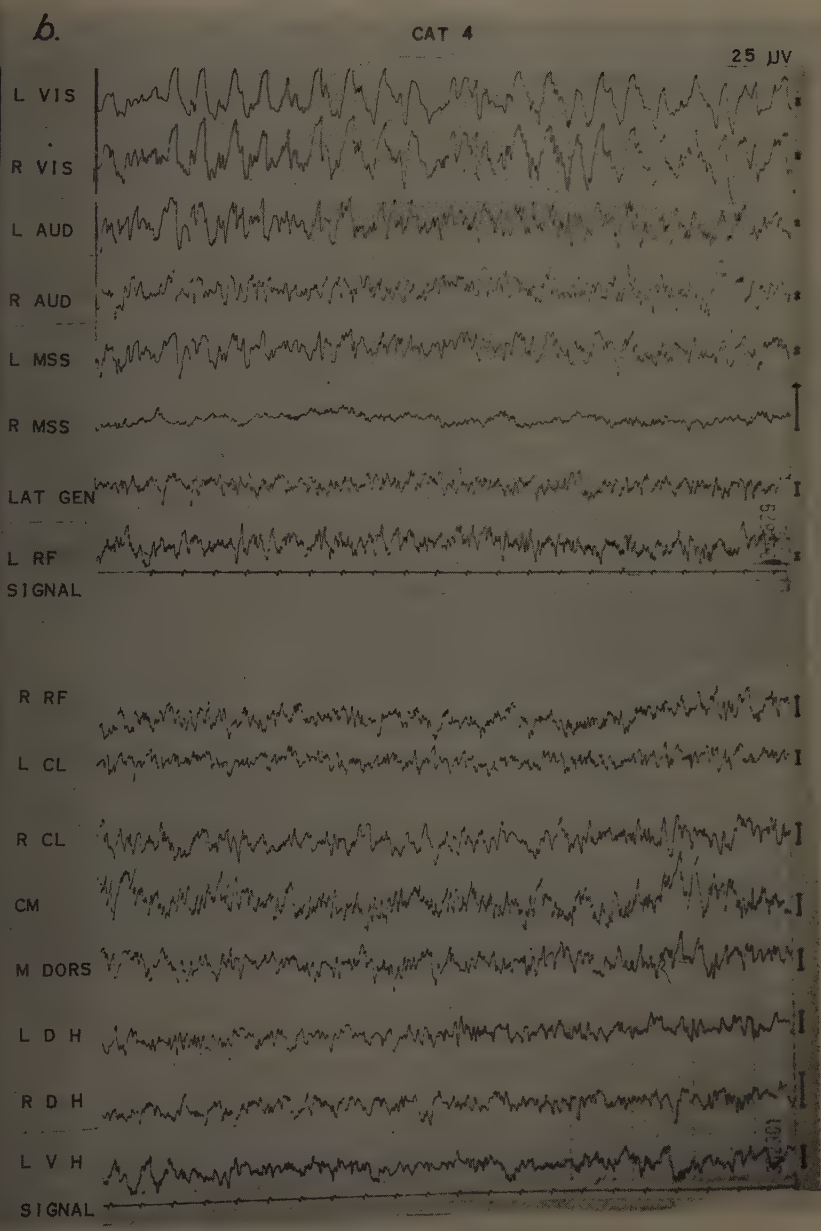


FIGURE 2. Response to 4-cps flicker before

response. As the generalized response tendency became replaced by well-differentiated response, the inhibitory 10-cps signal came to evoke a predominantly hypersynchronous slow activity rather than the previous frequency-specific response. Thus, slow waves seem to be related to inhibition in this case.



CAR training in Cat 10 (*a*) and Cat 4 (*b*).

FIGURE 6 shows the response of the two cats to the 4-cps flicker, which has an inhibitory significance for Cat 10 and serves as the positive stimulus for Cat 4. Both animals show marked slow waves in response to the 4-cps flicker. The lower set of tracings for Cat 10 illustrates an atypical cortical response

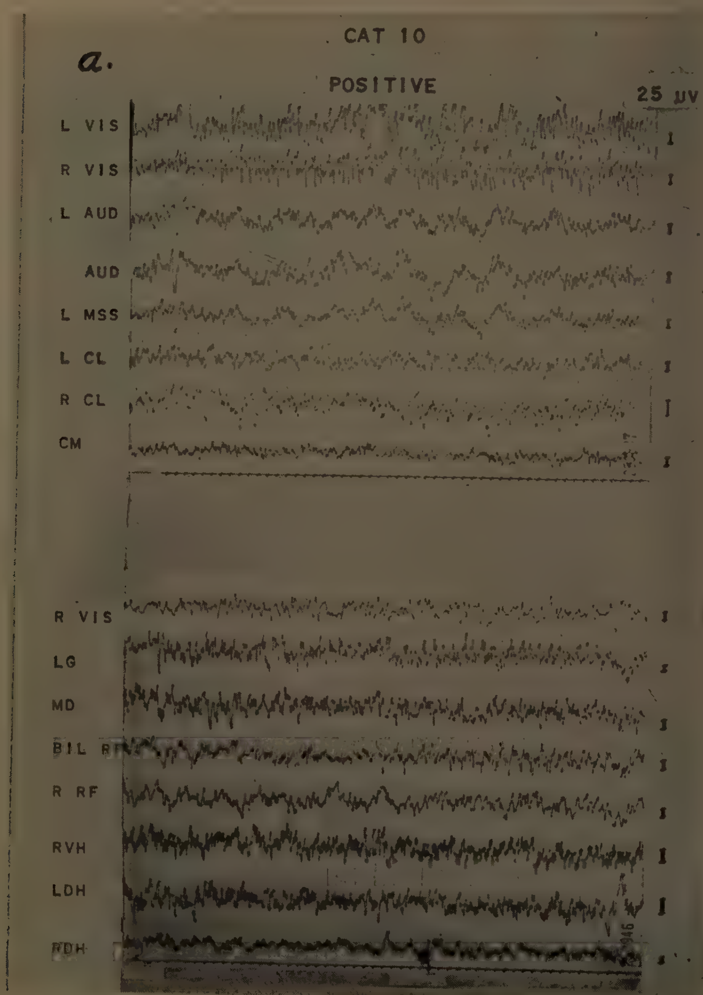
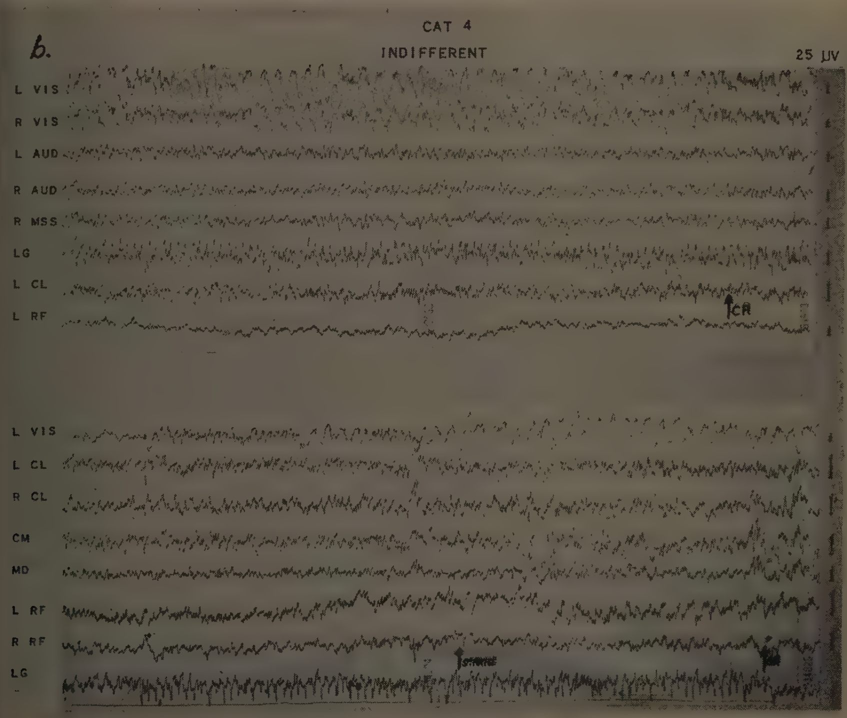


FIGURE 3. Response in Cat 10 (*a*) and in Cat 4 (*b*) to 10-cps

still associated with inhibition of the CAR. We see no clear difference between the two cortical response configurations that enables us to identify one as response to an inhibitory stimulus and the other as response to a positive signal. These data seem compatible with the suggestion that slow waves are necessary but not sufficient for inhibition to occur. Essentially similar conclusions are generated from experiments studying the effects of manipulations of the stimuli. We used a special circuit to delete every 10th pulse from the flickering light

presented to the cats. Our primary purpose was to ascertain whether, in the fully conditioned animal, exogenously derived electrical activity could be distinguished from endogenously derived electrical activity by the absence or presence in the waveform of a component corresponding to the pulse that was deleted from the stimulus train. (It seems worthwhile to mention that in some structures one can observe response at the time that the deleted pulse would have occurred, while in others this is not seen. This would appear to provide a technique to evaluate the contribution of endogenously generated activity, such as "assimilated rhythm," to the electrical response configuration of the trained animal.)

Of relevance to our present topic is the observation that presentation of the 10-cps flicker with the deletion of every 10th pulse ("limping" 10-cps flicker), after elaboration of differentiation, caused shift of the visual cortical response



flicker after CAR training, prior to differentiation (see text).

from 10 and 20 cps to 4 to 5 cps in Cat 10, and the CAR was inhibited. Conversely, in Cat 4 the CAR was elicited by the limping 10-cps flicker. These findings show that slow waves can be elicited by a rapid stimulus under circumstances indicating excitation in one instance and inhibition in the other.

Administration of LSD-25 to Cat 10 resulted in disinhibition of the CAR to the 4-cps flicker. Before LSD, 4-cps flicker elicited the CAR in zero out of 15 presentations. After LSD, 4-cps flicker elicited the CAR in 19 out of 24

presentations. In spite of the disinhibition, 4-cps flicker continued to evoke massive slow waves on visual cortex, although changes were noted in aspects of the configuration of electrical responses in other structures. These data further suggest that slow hypersynchronous cortical activity is not a sufficient condition for inhibitory function.

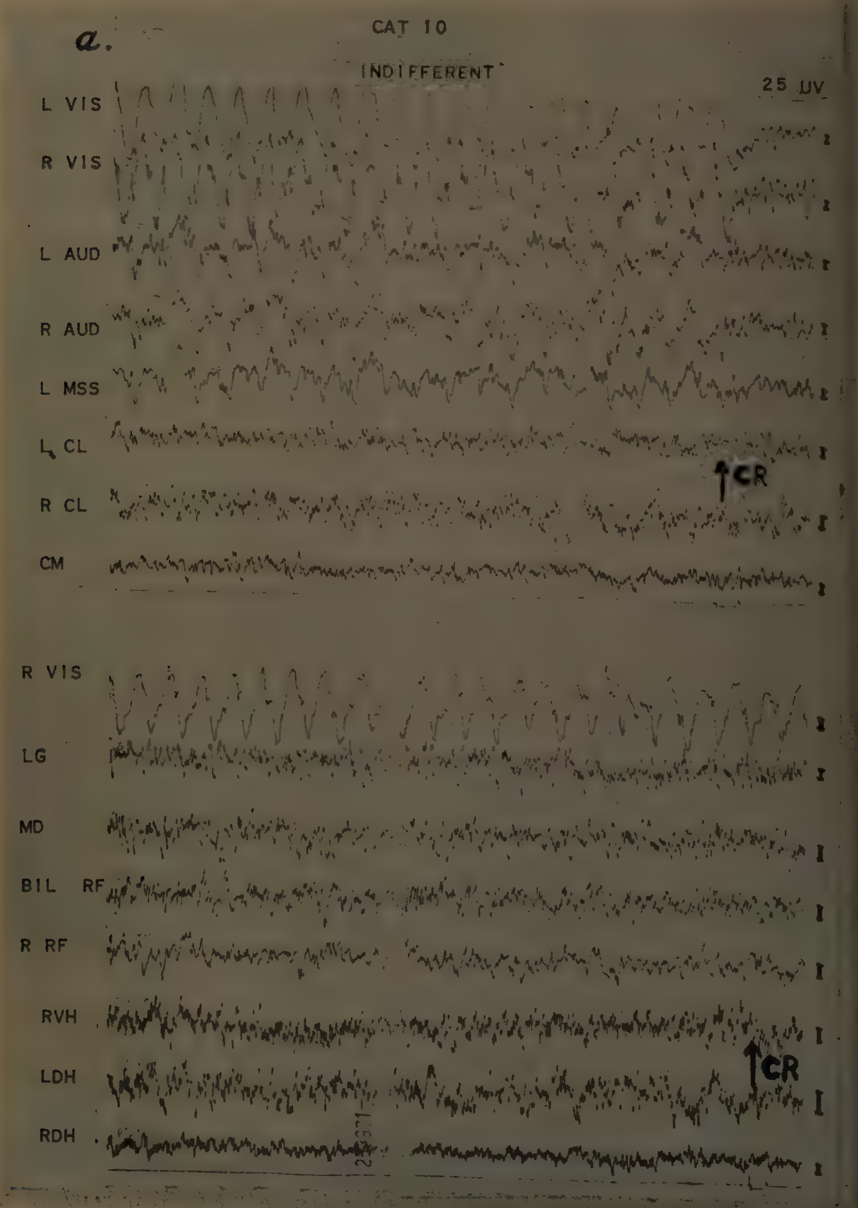
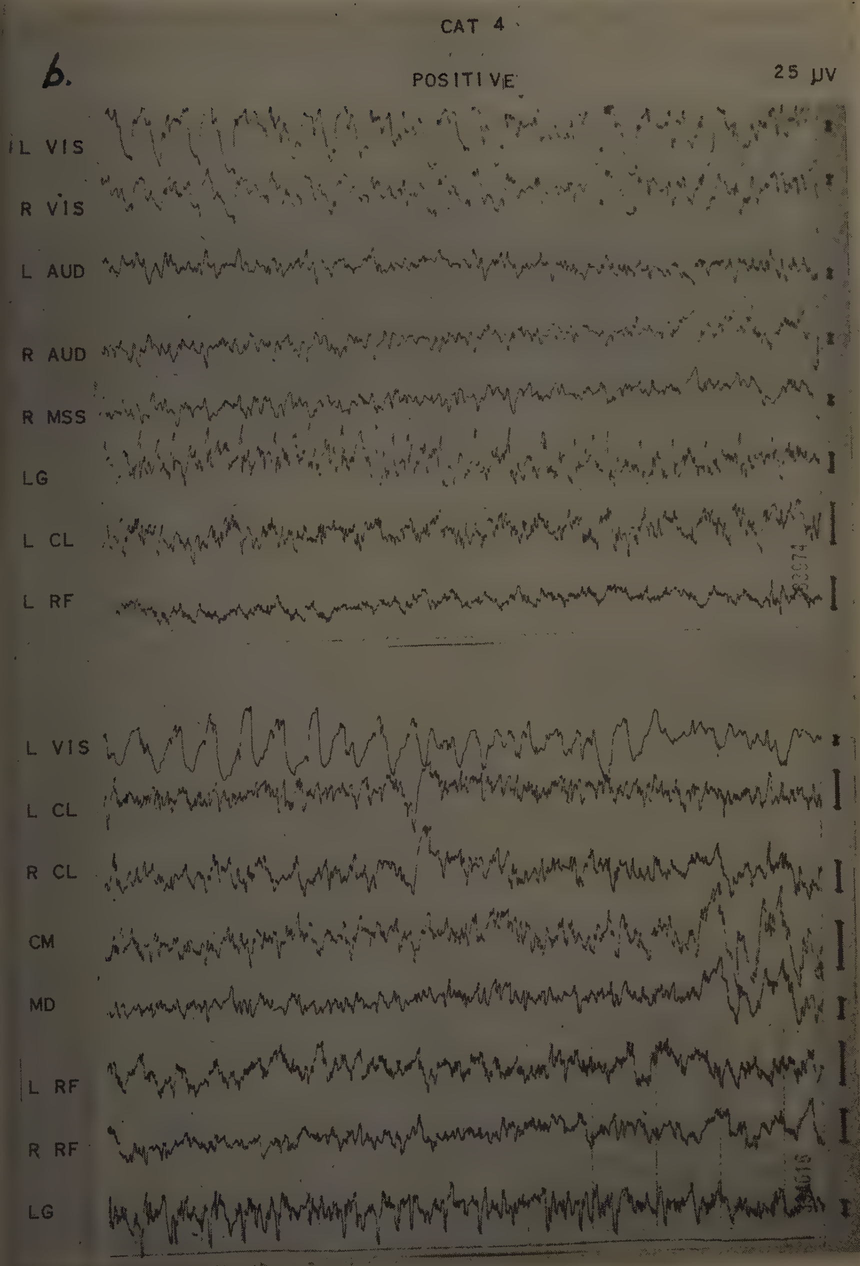


FIGURE 4. Response in Cat 10 (*a*) and in Cat 4 (*b*) to 4-cps



flicker after CAR training, prior to differentiation (see text).

In summary, then, cortical slow waves have been observed in circumstances related to excitation as well as to inhibition. No clear differences can be discerned between the cortical wave forms in these two cases that would enable us to differentiate them. Perhaps such differences would become clear with the use of an average response computer, or perhaps the crucial determinants of behavioral response are to be found in the subcortical components of the

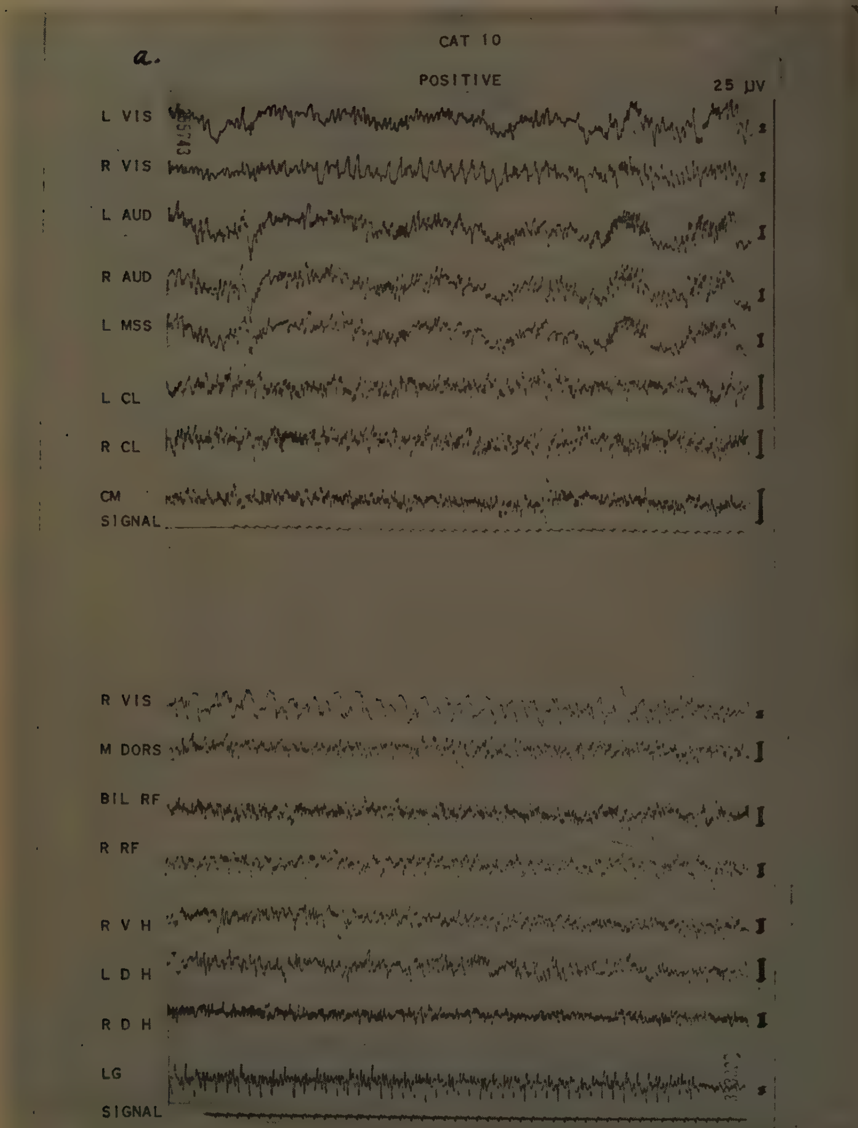
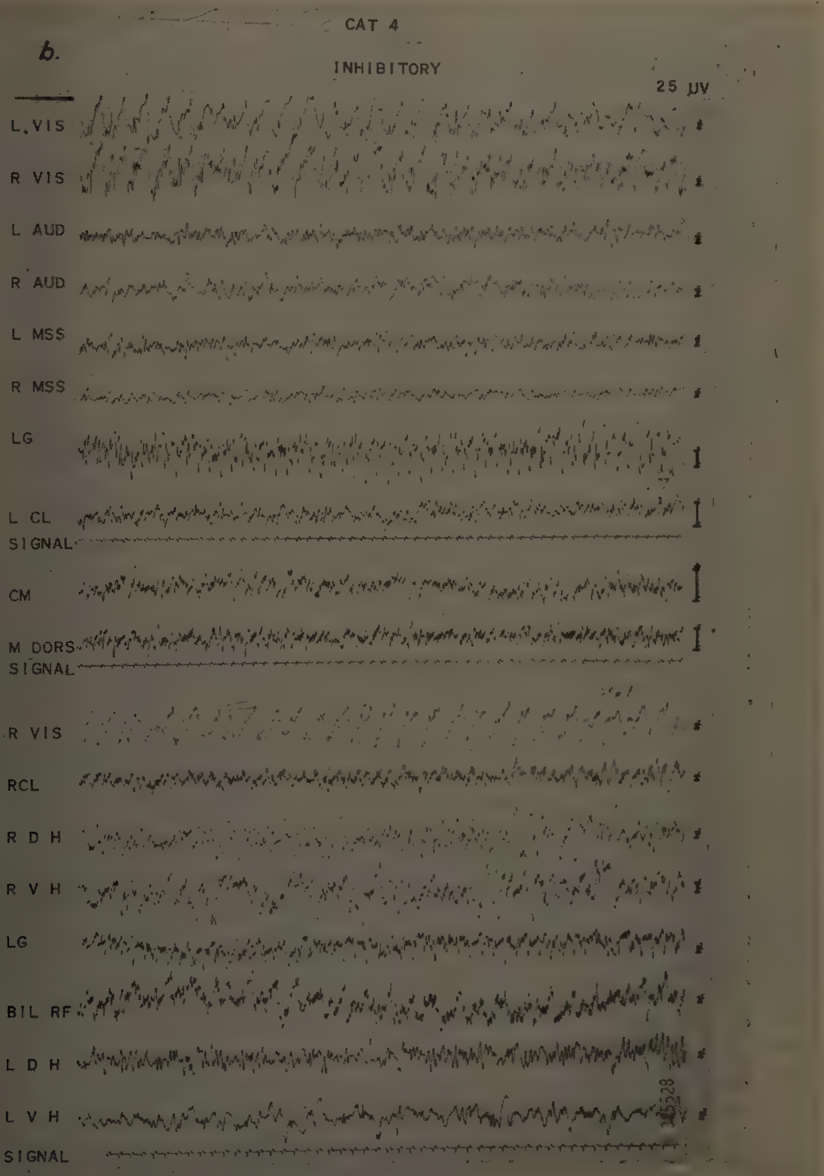


FIGURE 5. Positive correct response in Cat 10 (a) and inhibitory cor-

electrical response configuration. We have not yet examined closely that aspect of our data.

Our findings indicate that although the presence of massive slow waves is compatible with conditioned response performance, *inhibition of conditioned response is consistently accompanied by slow waves.* Cortical slow waves may



rect response in Cat 4 (*b*) to 10-cps flicker after differentiation.

be necessary but not *sufficient for such inhibition.* A number of other workers have presented evidence that the electrographic manifestation of internal inhibition is slow waves, appearing in response to the differential stimulus[9,19,17,8,23,10,7] or to the conditioned stimulus during behavioral extinction.[15,10,3,20,25] There is no uniform agreement as to the appearance of this phenomenon, since

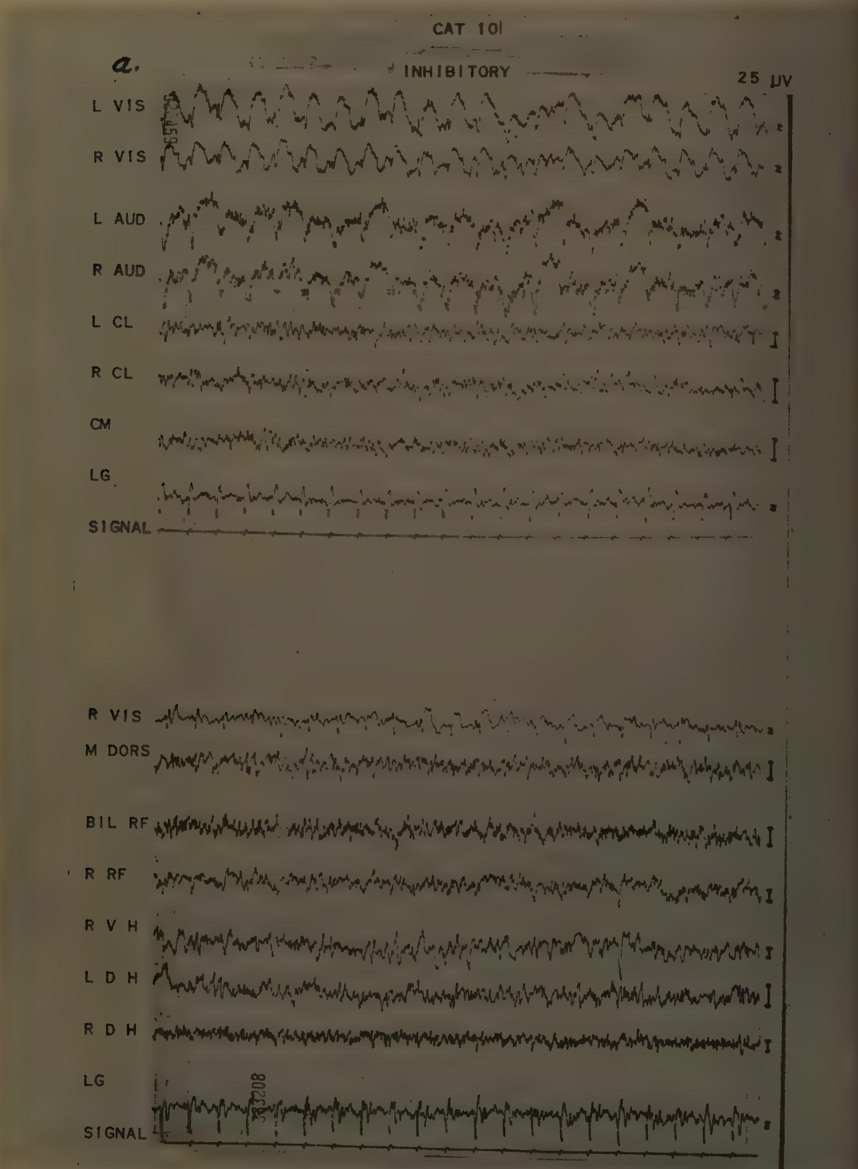
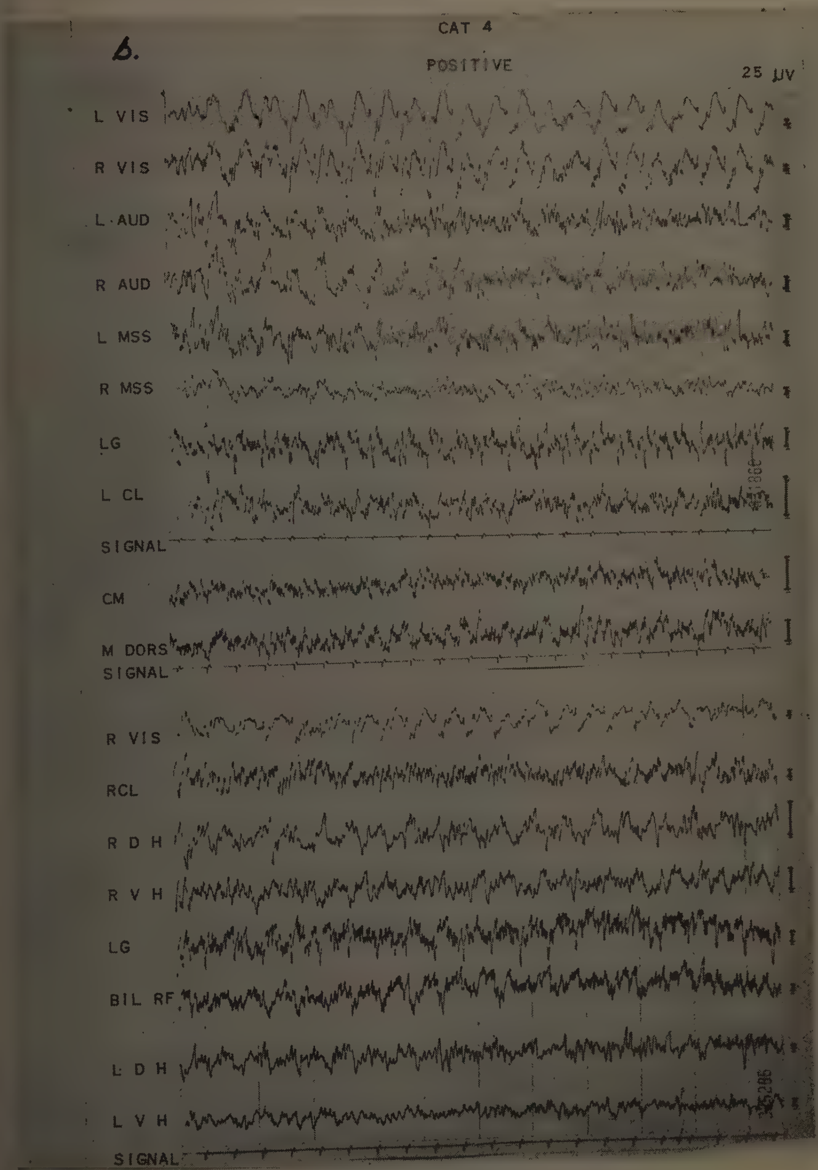


FIGURE 6. Inhibitory correct response in Cat 10 (*a*) and positive cor-

a number of authors have failed to confirm it.[5,2,1,21,22,15,24] This lack of unanimity may be due to the factors discussed earlier.

Several writers have interpreted this slow activity to be the electrical manifestation of internal inhibition, which was responsible for differentiation. Gastaut,[7] Grastyán,[10] Maeno,[17] and Yoshii *et al.*[24] have proposed that internal inhibition results from suppression of the reticular activating system. Grast-



rect-response in Cat 4 (*b*) to 4-cps flicker after differentiation.

yán[10] suggested that such suppression arises via hippocampal activation. Yoshii *et al.*[24] agreed with this formulation, and proposed that these hippocampal influences, mediated by the thalamic reticular formation, may exert their final inhibitory effects via a corticoreticular projection. On the basis of data of this sort, but emphasizing the inhibitory nature of surface negativity resulting from excitation of apical dendrites, Beritoff,[4] Kogan,[14] and Roytbak[20] have proposed that the essential mechanism of internal inhibition involves axodendritic processes that cause negativity of the apical dendrites of cortical pyramidal cells. These influences are presumed to originate in the thalamic reticular formation.

The results presented thus far suggest two possible interpretations of the functional role of the frequency-specific potentials observed in these and similar studies: (1) the appearance and frequency of such potentials is a reflection of generalized processes of excitation and inhibition; or (2) these potentials are related to the coding and processing of information about peripheral conditioned stimuli of corresponding frequencies. We have assumed that the appearance in a particular structure of potentials, at a frequency related to the frequency of the conditioned stimulus, indicated the arrival at that structure of information about the peripheral signal. We wished to evaluate the functional role that such frequency-specific potentials in a given structure played in the identification of the peripheral signal and the generation of the appropriate conditioned response. The results of a number of studies have suggested a good correlation between certain configurations of potentials and particular behavioral responses. Were these observed relationships of a causal nature, or were they only correlative?

We have tried to clarify this problem by investigating the behavioral consequences of presenting a conditioned stimulus to these differentially trained animals while, at the same time, we interfered with the response of a particular structure by stimulating it electrically. Since we are concerned not only with the involvement of a particular structure in mediation of the conditioned response, but also with the functional significance of the observed frequency-specific potentials, we have chosen as our central stimuli two wave forms that are intended to simulate the electrical responses observed to the two conditioned-flicker stimuli. Rather than ask simply whether perturbing the response of a structure by concomitant central and peripheral stimulation altered the performance of the conditioned response, we have investigated whether the disruptive effects of central stimulation with such simulated wave forms can be shown to be *differential* with respect to whether the simulated electrical input corresponds or disagrees with the conditioned stimulus, which is simultaneously presented to the animal.

Since our two cats were differentially trained to a 10-cps and a 4-cps flicker, we have chosen a simulated 10-cps and 4-cps wave form as our two central stimuli. Admittedly, these central stimuli can achieve only a primitive approximation to the normal physiological consequences of potentials of corresponding frequency recorded from a given structure. Pilot work showed us that central stimulation at slow frequencies corresponding to the observed potentials was essentially ineffective for our purposes. If we interpret EEG potentials as reflecting the integrated excitability influences impinging on the

monitored cell population, as summated dendritic potentials, then we might expect the over-all probability of nonrandom discharge of the elements in this population to covary with these modulations of excitability. We selected, therefore, a relatively fast pulse that was effective as a neural stimulus, and we amplitude modulated this *carrier pulse train* at the frequency of the conditioned stimulus whose effect we were attempting to simulate. While we obviously could not expect to reproduce the distribution of activity in a region that usually accompanied the appearance of an observed frequency specific potential, we might reasonably hope to affect the over-all probability of nonrandom discharge in that population by our crude simulation, in a roughly similar way.

We recognize that these various assumptions need not be valid, and that negative results in this endeavor will not permit definitive interpretation. Bearing this in mind, we shall describe our findings to date. We have explored a number of kinds of "carrier wave," and a number of modulation pulse widths.

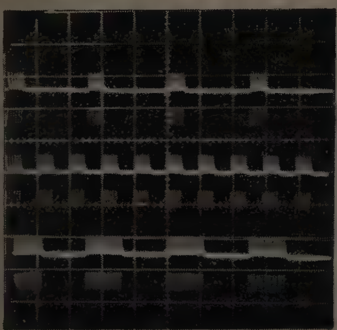


FIGURE 7. Wave forms for central stimulation.

In FIGURE 7 are shown the wave forms used in the collection of most of the results reported here. The carrier wave is a 100-cps biphasic square wave, of 2 msec. pulse width. The first and second tracings show a 4-cps and 10-cps modulated train, with a 50-msec. modulating pulse width. Since the pulse widths are the same in both instances, current flows for a total of 100 msec./sec. when using the 10-cps input, and for only 40 msec./sec. using the 4-cps wave form. We describe this pair of wave forms as a "power differential," since 2½ times more current flows with 10 cps than with 4 cps. The lower tracing shows a 4-cps modulation with a 125-msec. modulating pulse width, providing a total of 100 msec. of current flow per second of stimulation. We describe use of the middle and lower wave forms in conjunction as a "power match" in which total input per second is equated. By judicious use of power differential and power match, then, we can evaluate whether an observed effect arises from the frequency configuration or from the total power input of the simulated input, and decide whether the effect is due to a specific facilitation, disruption, or to coding.

The results are summarized in TABLE 1. Note that the data show, at a very

high significance level, that a 4-cps electrical stimulation of the visual cortex is much more effective than a 10-cps input in achieving inhibition of the CAR to a simultaneously presented CS in *both* Cat 10 and Cat 4, although the meaning of a 4-cps flicker is opposite for these two animals. Since this is true using both power differential and power match, we attribute this severe disrupting

TABLE 1
EFFECTS OF CONCURRENT STIMULATION

Structure	Cat	CS + central 4 cps +	CS + central 4 cps −	CS + central 10 cps +	CS + central 10 cps −	Current* (mAmp.)	Disruptive effects	P
BIL. VIS	4	12	3	11	3	3.4–4.0	=	—
	10	0	34	25	9	2.0–3.0	4 > 10	<0.001†
R. VIS	4	10	13	12	6	1.0–2.2	4 > 10	—
	10	5	26	27	4	2.1–2.5‡	4 > 10	<0.001§
L. VIS	4	20	69	62	25	1.0–1.7	4 > 10	<0.001†
	10	12	19	31	0	3.2–4.8	4 > 10	<0.001§
BIL. MSS	4	17	0	13	1	1.0–2.0‡	=	—
	10	17	4	16	5	1.35–3.0‡	=	—
BIL. AUD	4	3	9	7	5	1.0–1.9	4 > 10	—
	10	25	18	20	23	2.3–3.2	10 > 4	—
LG	4	39	61	26	43	0.2–1.0	=	—
	10	15	45	34	25	0.96–1.25	4 > 10	<0.001§
BIL. DORS H	4	9	1	3	10	0.13–0.36	10 > 4	<0.01¶
	10	3	8	0	11	1.1–2.1	10 > 4	—
BIL. VENT H	4	4	3	5	0	0.18–0.38	4 > 10	—¶
	10	17	7	9	15	1.0–1.15	10 > 4	<0.05§
BIL. RF	4	27	20	23	23	0.1–0.36	10 > 4	—
	10	30	23	18	35	0.28–0.36	10 > 4	<0.05§
BIL. CL	4	14	10	10	16	0.2–0.4	10 > 4	—
	10	16	25	13	28	0.45–1.0	10 > 4	—
CM	4	19	36	17	36	0.2–0.25	=	—
	10	42	64	38	69	0.70–0.85	10 > 4	—
MED. DORS	4	3	1	2	1	0.16–0.24	=	—
	10	21	16	7	30	0.48–0.68	10 > 4	<0.001¶

* The upper current value represents the occlusion threshold.
† Equally significant with power match.
‡ No occlusion threshold found.
§ No power match data.
¶ Not significant with power match.

effect to the frequency of the simulated input. Four-cps input is much more inhibitory than 10-cps input. Note that this effect is not observed on auditory or medial suprasylvian cortex, but seems relatively specific to the cortex of the CS modality. This suggests that the input in some way interferes with activity in the visual system, and that the visual cortex or regions to which it projects are involved in the mediation of the CR. These results are difficult to reconcile with the ability of Cat 4, for example, to sustain appropriate conditioned

performance to 4-cps flicker when 2½ times as much current is presented to the same visual cortex at 10 cps.

Our results, then, support a number of conclusions and raise a number of problems. Our electrographic data indicate that *cortical slow waves are associated with inhibition, although they do not preclude excitation.* The results of concurrent central and peripheral stimulation show that a 4-cps cortical input is severely disruptive when compared with a 10-cps input. Slow cortical activity can apparently cause inhibition. If such slow activity is inhibitory when applied directly to the visual cortex, why is it not necessarily inhibitory when derived from visual stimulation with the CS? The answer may lie in a detailed examination of the different spatial distribution of the cellular processes affected in the two cases. It may be that the surface electrical stimulation results in preferential activation of superficially located presynaptic processes with a subsequent selective activation of axodendritic synapses, causing a shift in the postsynaptic potential distribution from that caused by more physiological input. This does not explain the dependence of these effects upon frequency.

The differential inhibition of CAR by 4-cps stimulation of the lateral geniculate in Cat 10 was exceedingly reliable. The absence of any differential effect in Cat 4 under similar circumstances is difficult to explain. With the exception of this structure, no subcortical structure showed either a significantly more inhibitory effect of a 4-cps input, or a trend in that direction. Since hippocampus, mesencephalic reticular formation, and nonspecific thalamic areas were explored bilaterally in some detail, with consistent failure to observe differential inhibition arising from 4-cps input, our data do not provide support for the suggestion that the inhibitory cortical slow waves arise as a consequence of slow activity propagated from these structures to the cortex, or vice versa.

Finally, the results of this admittedly crude and exploratory pilot study do not provide evidence that the configuration of frequency-specific potentials observed in these structures during performance of the CAR to the appropriate flicker CS are the coded information about the peripheral CS being transmitted and processed by the nervous system. The techniques described herein are being applied and extended in continuing studies in our laboratory to explore further the central mechanisms involved in coding and processing information about differentially conditioned stimuli.

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DAY-TO-DAY VARIABILITY IN RELATIONSHIP BETWEEN ELECTROENCEPHALOGRAPHIC ALPHA PHASE AND REACTION TIME TO VISUAL STIMULI*

Enoch Callaway III

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E. A. Asratyan has presented us with an admirable example of scientific work. It is always a pleasure to see a problem so clearly defined and so elegantly attacked. This paper is particularly exciting because the problem is familiar—in this case the ubiquitous "confounded problem of inhibition"—but the approach is somewhat unfamiliar.

Asratyan first considers that conditioned inhibition may originate in either the locus of the conditioned stimulus, or else in the locus of the unconditioned stimulus. Although local effects of conditioned inhibition are observed at cortical foci, the data force him to locate the origin of inhibition in the diffuse and plastic connections between conditioned and unconditioned stimuli. Asratyan would apparently prefer to view the central nervous system in terms of more or less discrete couplings that reflect environmental forces, but he also follows his experimental evidence with true scientific curiosity. There is even one mention of Konorski's view that there is a special inhibitory structure, although nothing more is said about the possibility of more or less autonomous and diffuse inhibitory functions.

In this country there are some who prefer more emphasis on diffuse and autonomous central nervous system functions. Words such as motivation, attention, and cognition figure prominently in our theories, and we often seek evidence for action of the central nervous system on the relationship between stimulus and response, until our data remind us that repeated pairing of stimulus and response may modify these relatively autonomous functions.

Consider the question of how the organism operates on incoming sensory data. Do generalized fluctuations in gross behavior parallel the 8- to 13-cps fluctuations in brain potential known as the alpha rhythm? If so, does this reflect some diffuse inhibitory cycle that operates in encoding and ordering stimuli? Such speculations are suggested by Lindsley's[1] comments on the "Neuronic Shutter," and by Freud's[2] ideas about a discontinuous perceptual system.

To bring these speculations into the laboratory, my colleagues and I seat a person with his eyes closed, and we have him press a key immediately whenever a bright light is flashed in his face. The apparatus is somewhat complex; a preliminary report is in press.[3] Here I shall say only that we can cause the light to flash at selected phases of this person's alpha cycle, and that we can accurately and automatically record the interval between each light flash and response. By collecting data on sufficient numbers of responses to stimuli

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presented at various phases of the alpha cycle, we can show changes in reaction time that parallel changes in this particular form of brain potential.

A sample of our data is shown in FIGURE 1. These are three experiments from the same subject. Each point represents the average of about 40 reaction times to stimuli presented at the corresponding phase of the alpha cycle

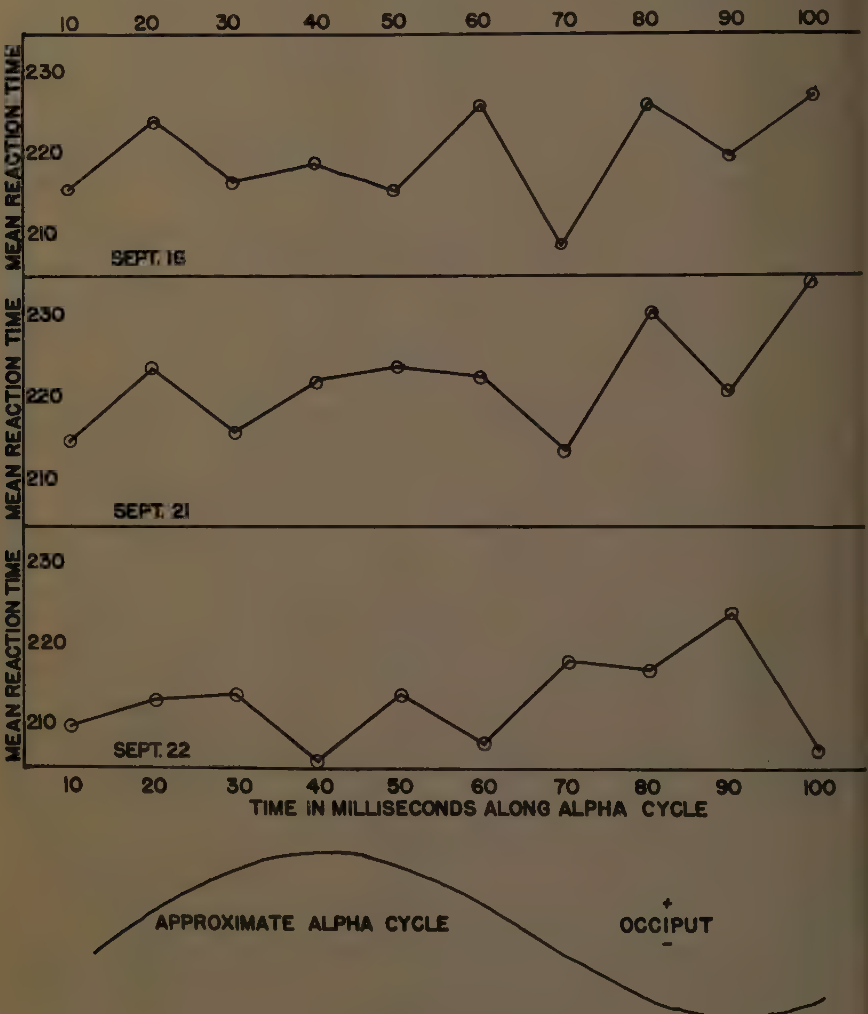

FIGURE 1.

shown at the bottom of the figure. There is a cyclic slowing of reaction time, and at first we took this as evidence for a cyclic, diffuse, autonomous inhibitory process. However, just how diffuse is this inhibitory process? We find a parallel between reaction time and alpha phase only when we use visual stimuli. Thus far we have been unable to demonstrate any variation in reaction time when auditory signals are presented at various phases of the alpha

cycle. Moreover, just how autonomous is this inhibitory cycle? Note in FIGURE 1 that as the subject is tested again and again, stimuli at the alpha phase 60 msec. from our reference point elicit progressively faster reaction times.

The statistical validity of this variable relationship between alpha phase and reaction time was checked by a 3 × 10 analysis of variance, although disproportionate subclass numbers necessitated approximate fitting of constants, as described by Snedecor.[4] The results are summarized in TABLE 1. The significant interaction term indicates a relationship between alpha phase and reaction time that varies from day to day, possibly with increasing experience on the part of the subject.

More work must be done, but from the data at hand we must consider two possibilities. First, the "diffuse" process reflected by the alpha cycle may not be so diffuse: it may be more or less specific to the visual system. Second, the "autonomous" effects of whatever the alpha cycle reflects may not be so autonomous. These effects may be very much a function of the experience of the organism.

TABLE 1

SIGNIFICANCE OF VARIATIONS IN REACTION TIME SHOWN IN FIGURE 1

Source	d.f.*	Mean square	F*	$F_{0.05}$*	$F_{0.01}$*
Phases	9	.000, 050, 299........	2.625		2.43
Days	2	.000, 290, 244........	15.147		4.62
Interaction	18	.000, 036, 349........	1.897	1.65	2.10
Error	1154	.000, 019, 162........			

* Key: d.f., degrees of freedom; F, the ratio between variances obtained by analysis of variance; $F_{0.05}$, the F ratio required for a 0.05 level of confidence (that is, a ratio between variances that would be expected, by chance, five times in each 100); and $F_{0.01}$, the F ratio for the 1 per cent level of confidence.

In science, theoretical bias determines the problem to be studied and the method of approach. Thus theoretical bias determines what results will be obtained. Nevertheless, when one does experiments the data are likely to lead beyond current theories. In such an event, the results obtained by others who are guided by quite different views of the world become particularly valuable.

Therefore, in closing, may I express my gratitude for the opportunity afforded by our collaboration in publishing this monograph of becoming better acquainted with our Soviet colleagues and their stimulating scientific work. Our views of nature may be different, but in the words of Pavlov, "Success in deciphering nature's crowning achievement, the action of the brain, demands absolute freedom, total disavowal of stereotype, and all possible diversities of points of view and methods."[4]

Acknowledgments

I am indebted to Pat Compton for technical assistance and to Sanford Autumn for statistical evaluation of the data.

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DISCUSSION: PART VI

KENNETH W. SPENCE (*State University of Iowa, Iowa City, Iowa*): As a psychologist whose special field of interests lies solely in behavioral phenomena and not in its neurophysiological basis, I find myself unable to comment in any specific manner on the research studies presented in these pages. Instead, I should like to record a brief methodological note concerning the influence that the man we honor on this occasion, I. P. Pavlov, had upon the development of modern objective psychology in the United States. More particularly, I should like to call attention to the important role that the writings of Pavlov played in the *behavior theory* approach to simple learning phenomena, including conditioning, developed at Yale University, New Haven, Conn., by Clark Hull and those of us allied with him.

The Pavlovian influence upon our work was such, in fact, that the late Karl Lashley a number of years ago fell into the habit of designating Hull, myself, and others of our group as neo-Pavlovians. While I am sure that Hull felt, and I know that I did, that the designation was a great compliment, I have always had serious reservations about it: first, as to whether Lashley intended the designation to be complimentary and, second, whether, whatever Lashley's intention, Hull and I really deserved the label and, if we did, in what sense.

I should not want to be misunderstood in this matter. It is certainly true that in turning his attention in 1929 to the area of learning, Hull was greatly influenced by the timely G. V. Anrep translation of Pavlov's Petrograd *Lectures on Conditioned Reflexes*.[1] Thus in his articles in the 1930s Hull made considerable use of such Pavlovian concepts as excitation, inhibition, and generalization. Moreover, he enthusiastically undertook experimental studies employing various conditioning techniques. However, whereas the interest of Pavlov and his colleagues in these experiments was in the knowledge they might provide as to the nature of the activity of the central nervous system, particularly its higher cortical divisions, Hull's and my interests were in the laws of conditioned behavior per se.

Our interest in these laws, in turn, had as its basis the belief that the simple type of behavior represented in classical and instrumental conditioning provided the best source of information for making inferences concerning the possible theoretical events assumed to underlie behavior changes occurring in different learning situations. That is, in contrast to the more complex types of learning situations in which the response measures are a function of two or more competing action tendencies, we believed that the conditioning experiment provided a situation in which the response measures reflected the strength of a single S-R tendency more or less in isolation from other S-R tendencies. Hence we assumed that the behavioral laws relating the changes in response strength with reinforcements and nonreinforcements in the conditioning type of experiment reflected more directly these hypothetical processes than did more complex learning experiments.

At any rate, on the basis of the empirical laws obtained in these conditioning studies we attempted to develop a theoretical schema consisting primarily of abstractive concepts, the so-called intervening variables, familiar examples

of which are habit strength (H), drive strength (D), excitatory potential (E), and inhibition (I). This theory has not only had the purpose of explaining, in the sense of deducing, the known quantitative findings of simple conditioning experiments, but has also been employed to derive quantitative implications concerning behavior in more complex types of learning situations. In other words, the primary objective of our work has been to discover a set of *abstract theoretical concepts* that would serve to integrate and bring into deductive relation with one another the many specific behavior laws found in a wide variety of learning situations.

The question naturally arises as to what the relation of these concepts abstracted from behavior data is to neurophysiological concepts or processes. Hull, it will be recalled, was fond of attempting to make such tie-ups. Thus he related his concept of habit strength (H) to the strength or degree of conductance of a receptor-effector connection. Actually, however, Hull made little or no use of such coordinations in his research program, apparently suggesting them merely as hints or guides to interested physiological psychologists. In contrast to Hull, I have never had a strong compulsion to engage in such thinking, although it is true that in recent years I have had a tendency to flirt with such physiologically sounding concepts as my hypothetical emotional response (r_e) as the basis of generalized drive level (D). As I stated earlier, however, I have not attempted to relate systematically our intervening variables to possible neural processes or events and, with my lack of up-to-date knowledge on such matters, I am hardly in a position to state whether attempts at such coordination are at present fruitful or even feasible.

Returning to Pavlov, or at least to that portion of his work with which I am familiar, it is interesting to note that his theoretical concepts appear to have been, in part at least, like our behaviorally inferred concepts and, in part, to have involved hypothesized neural functions. Consider, for example, his concept of *internal inhibition* as elaborated in his 1924 Petrograd lectures. Pavlov's specification of the properties of this notion was primarily in terms of observed changes in the strength of CRS that occur with various experimental operations (for example, nonreinforcement, differentiation, and delay). Thus internal inhibition was assumed by him to increase in amount with successive omissions of the UCS because the CR decreased in magnitude. Again, it was assumed to dissipate in time because the CR spontaneously recovered in strength with the passage of time and for other reasons. In other words some of the properties of the construct were defined in terms of measured changes in the overt behavior of the subject, not in terms of any kind of measurements (electrical, chemical, or such) of neural processes or nervous tissue. Indeed, to the best of my memory, there were no adequate measurements of the activities of the cortical cells during conditioning in this early period of research. Lacking these, Pavlov offered other neurophysiological hypotheses, such as that the inhibitory process was located in the cortical cells of the sensory analysers corresponding to the CS, that the two processes interacted or limited each other's action, and that they both irradiated to other cortical areas and also exhibited concentration. While Pavlov and his early co-workers did do some extirpation work and also employed drugs, for the most part these

speculations as to the nature of the cortical events were primarily guided by the purely behavioral findings in the various conditioning experiments.

In this connection it has been interesting to note that in the tradition of Pavlov, E. A. Asratyan and his colleagues have also relied heavily on purely behavioral studies of conditioning to test their physiological theories.

This difference in aim between Pavlov and the Soviet scientists who have followed him on the one hand, and the behavior theorists in the United States who have directed their research towards conditioning phenomena on the other, brings me back to my opening remarks. I have long suspected that Lashley did not have a very favorable view of these speculative concepts of Pavlov concerning the activities of the cortex. In his rejection of this portion of the Pavlovian theory, which may at that time have been quite justifiable since the concepts were highly speculative, Lashley seems not to have been aware of the properties of some of these constructs that were abstracted from the behavior laws obtained in the experimental studies. It is the latter type of concept that Hull and I have attempted to exploit; and it is in the sense that Pavlov was the first to demonstrate the manner in which such constructs are derived from a series of carefully planned systematic experiments that Hull and I regarded, indeed have prided ourselves, on being neo-Pavlovians.

Reference

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Gregory A. Kimble (*Department of Psychology, Duke University, Durham, N. C.*): Recently I have become interested in a phenomenon of eyelid conditioning that appears to resemble what Kupalov calls the pathological irradiation of inhibition. This phenomenon consists of the marked diminution of the unconditioned eye-blink when it is elicited in the presence of the conditioned stimulus. Figure 1 presents tracings of a series of eye-blink records taken from a human subject in an eyelid-conditioning experiment run according to the following plan. After the usual pretests with conditioned and unconditioned stimuli alone, there was a series of 20 trials in which the CS (a dim light) and the US (corneal air puff) were paired. Trials 21 to 25 consisted of stimulations with the US alone. Trials 26 to 30 again consisted of paired presentations of CS and US. The panels in figure 1 are representative of the responses obtained in the various parts of this procedure.

Note that, beginning with the initial test trial and proceeding through Trial 20, there is a progressive diminution in the amplitude of the UR. This reduction might be regarded as reflex habituation were it not for the evidence to the contrary obtained on Trials 21 to 25, two of which are shown in figure 1. Note that on Trial 21, without the CS, the reflex regains full strength and maintains it on all trials with the US alone. On Trial 26, when the CS is presented again, there is a reduction in response strength to a small fraction of its value on Trial 25. The records taken from Trials 26 and 30 are typical. In no case did the unconditioned reflex attain its original strength on trials when the CS was presented.

The implication here is that, whatever the process involved, it is under the

control of the CS. The experimental work of my co-workers and myself has consisted of efforts to find out more about this phenomenon. In the first of our experiments we studied the relationship of this inhibitory process to the interstimulus interval. In this study there was a total of 64 subjects divided into four groups. Each group was conditioned at a different interstimulus interval: 0.25 sec.; 0.50 sec.; 1.0 sec.; and 2.0 sec. Each subject was run for one session and received the following trials: (1) five test trials with the CS; (2) five trials with the US, to determine the initial amplitude of the reflex; (3) 50 conditioning trials with the CS and US paired at the appropriate interval; and (4) 10 trials with the US alone again. Our chief interest was in a

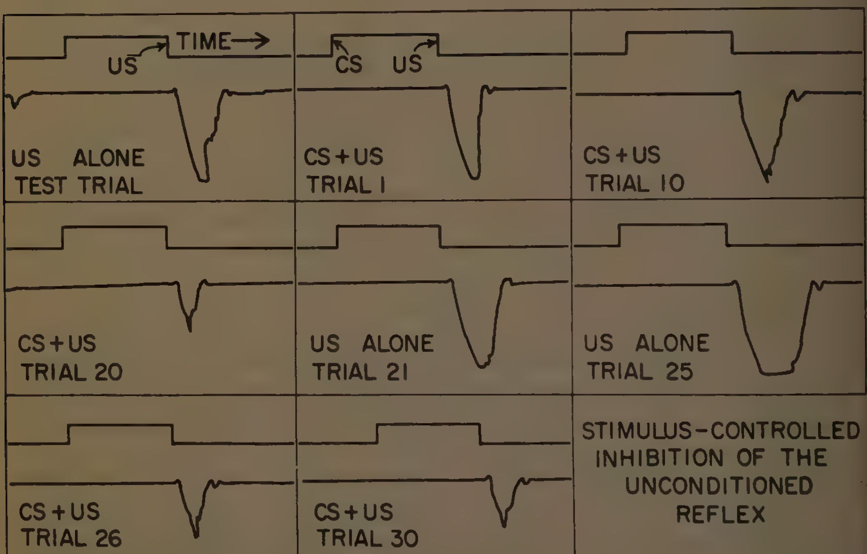

FIGURE 1. The upper line records onset of light (CS) and air puff (US). For purposes of making essential measurements the signals for these events occur on all trials, even if the stimulus was not presented. Note the decrease in amplitude of the UR that appears most markedly on Trials 20, 26, and 30. On Trials 21 to 25, without the CS, the reflex regained its normal strength.

comparison of the amplitude of the URs at the end of conditioning and during subsequent trials without the CS. Somewhat to our surprise, the function emerging from this study was one that exactly paralleled the usual function for the relationship between conditioning and the interstimulus interval; that is, the magnitude of the inhibitory process was greatest when conditioning occurred at a CS-US interval of 0.5 sec., and less at either shorter or longer intervals. Later we found out that the effect occurs in the records of individual subjects. FIGURE 2 is a record taken from a single subject who was tested at all of these intervals. The reduction in the amplitude of the UR on trials with 0.5 sec. between the CS and US is quite obvious. This means that the inhibitory effect is strongest at the very same temporal point as the (excitatory) tendency to make a conditioned response.

Pursuing our inquiry into the nature of this inhibitory process somewhat further, we have found that it is related to individual differences. In brief, some subjects show the effect rather markedly, while other subjects show the opposite effect; that is, in the absence of the conditioned stimulus some subjects' unconditioned reflexes are somewhat weaker than in the presence of the conditioned stimulus. On the basis of evidence such as this we have been led to wonder whether we may not have discovered in human subjects a differ-

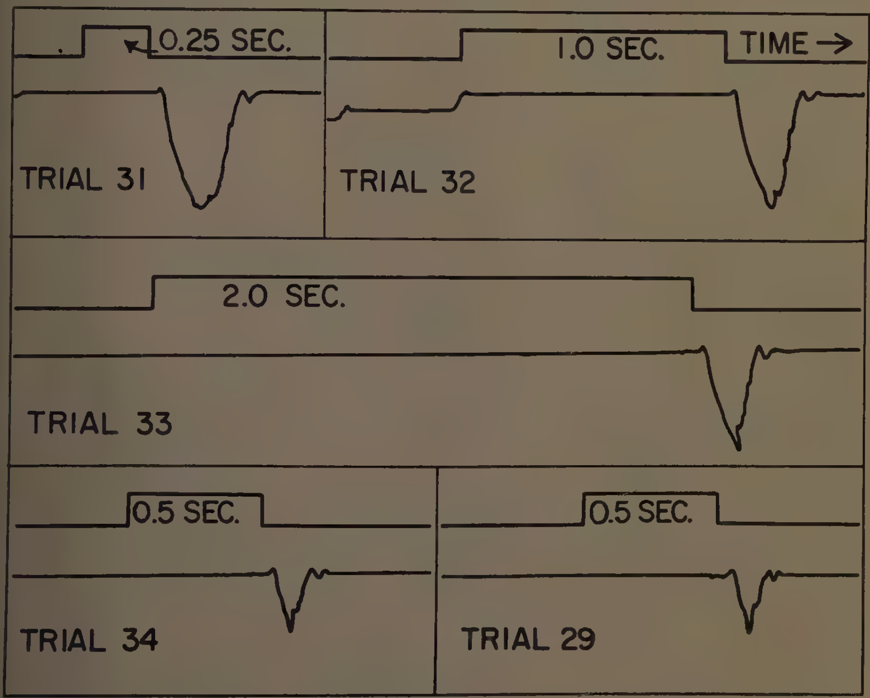

FIGURE 2. Trials 31 to 34 were selected because the four test intervals occurred in sequence in these four trials. Thus no bias is introduced by the selection of records. Trial 29 was the next to the last in a series of 30 trials with a 0.5-sec. interval. The record on Trial 30 was not used because it was marred by random blinks.

ence that parallels that originally noted by Pavlov in dogs. It looks very much as if at the human level, too, there are excitable and inhibitable organisms. Subjects who show the inhibitory effect in very great strength typically do not develop conditioned responses. Such facts have led us to speculate whether the inhibition involved might not be the same as the Pavlovian inhibition of delay, extending forward in time to the point at which it inhibits not only the conditioned reflex but also the unconditioned reflex as well, much as Kupalov describes it in his paper. If this were the case, one might expect two phenomena to appear. In the first place, one might anticipate that a subject who shows this inhibitory phenomenon in great proportions, while giving no

conditioned responses at the usual optimal interval of one-half second, might display conditioned responses at a longer interval. A second expectation is that an extra (disinhibiting) stimulus might lead to the appearance of conditioned responses in the interstimulus interval.

Thus far we have not examined these possibilities systematically. We have, however, tried the indicated experimental operations informally on a few subjects with results that are encouraging. FIGURE 3 presents a series of typical records taken from a subject who did not condition well at 0.5 sec.,

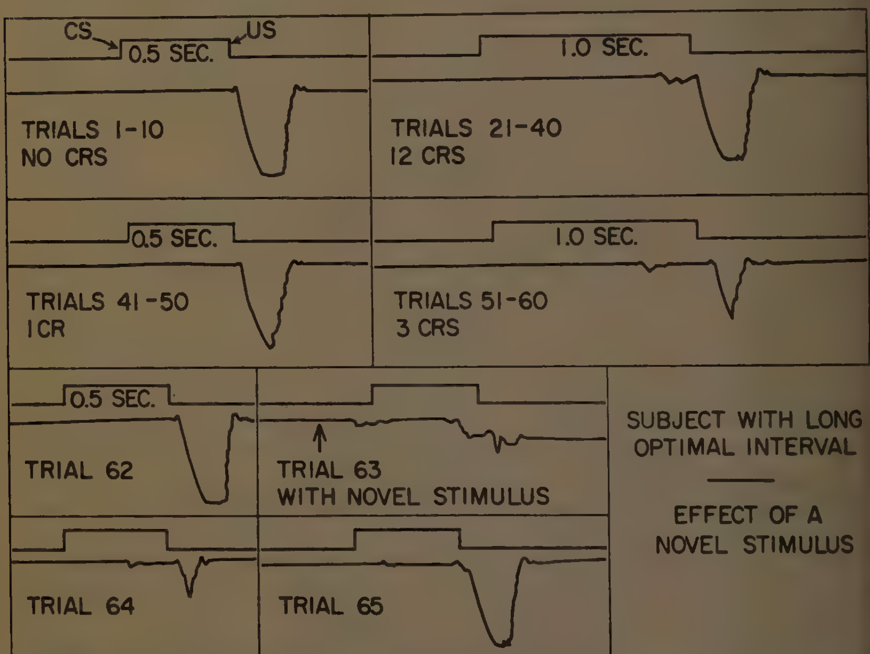

FIGURE 3. The records are typical of the blocks of trials in question. Those with 0.5-sec. intervals have only unconditioned responses. Conditioned responses appear on the records for the 1.0-sec. trials. The disinhibiting stimulus was presented only on Trial 63. Its effect, however, persisted on Trial 64 and, perhaps, on Trial 65.

although he did not develop a substantial amount of stimulus-controlled inhibition either. Examination of the series of records presented in FIGURE 3 will show that our two expectations were realized: (1) extending the interstimulus interval to a full second produced a good many more conditioned responses than occurred at half a second; and (2) adding a disinhibiting stimulus (produced by raking a plastic ruler across the face of the intercommunication system between the experimenter and the subject) produced a disinhibiting effect which persisted for a number of trials. Unfortunately this subject was not one of those who showed a marked diminution in the amplitude of the UR. Only further work will make it possible to tell whether the preliminary results presented in FIGURE 3 and the inhibitory mechanism are related.

KARL PRIBRAM (*Stanford University Medical Center, Palo Alto, Calif.*): Throughout the pages of this monograph we have been plagued by some terminological discordances. The term inhibition is a case in point. Very often the wolf inhibition, derived from behavioral observations, poses in sheep's clothing as a neurological phenomenon. At other times the wolf appears as wolf and, at still other times, one sees the peaceful scene of many sheep grazing in the neurological convolutions. Let us consider two papers. One, strictly behavioral, by E. A. Asratyan, beautifully supports his concept that something goes on in the temporary connection formed between two behavioral events and that neither of the behavioral events is inhibited per se. E. Roy John, on the other hand, has dealt with the neural events and described the difficulties of inferring inhibition of neuronal activity from the direct electrical recording of slow activity. Kenneth W. Spence, in his discussion, gave us some insight into the methodological problem before us. He suggests—correctly—that we keep the behavioral phenomena and inferences made from them separate from the neurological phenomena. With this I agree. One quarter of a century ago Spence outlined this position as the $S \rightarrow O \rightarrow R$ position. It seems to me that Spence is now somewhat unhappy, however, because he feels uneasily that all of behavior may *not* be understood by taking into account *only* the situational stimulus variables. Yet he does not feel that the answer is the one prevalent in these pages. Here the intervening variables defined by conditioning and learning theorists are being treated as if we expected them to turn out to be constructs that can be neurologically identified. Spence rightly feels that we should not go hunting in the nervous system for behaviorally derived concepts. Have we not had enough of this sort of thing over the past century?

There is a way out. Spence and other psychologists, including Neal Miller, tend to look at the organism as a system of variables *intervening* in a series between stimulus and response. However, as their electrophysiological colleagues so effectively demonstrate in this monograph, the organism can be treated as a system of variables in *parallel* with those in the environment. Behavior can be studied as the resultant of the *inter*action of two classes of variables: organism and environment. This is physiological psychology as I conceive it. There is no hunt for intervening process; there is direct examination and manipulation of these processes as they affect behavior. All psychology must not be physiological psychology but, as Magoun's paper indicated to us so clearly, studies in the field of learning can well afford by now to take into account the neurological phenomena demonstrated in the laboratory. A true physiological psychology is in the making. We need not resort to the neurologizing of behaviorally derived constructs. As Kline has told us, a little clear thinking in this area will do a great deal to make possible the rapprochement between studies of the conditional reflex, of instrumental learning, and of the neurological phenomena. The Pavlovians, especially, have been guilty of drawing ambiguous referents from their data, although Pavlov himself was clear. For instance, as we all know, Pavlov pointed out that inhibition at the behavioral level might well turn out to be a very active process in the brain. My plea, therefore, is: let us talk about psychological processes when we are talking about behavioral data, about neural processes when we have made ac-

tual observations on the brain, and about correlations between the two only when we have both. Again, as we saw from Roy John's paper, when we enter this difficult area we are due for some surprises. But of course it is these surprises that lead to the new advances that make this field so alive.

One other point: there may be another error that we are all prone to commit. We think of behavioral science as unitary and neurological science as unitary. Thus a behaviorally derived concept, inhibition, is compared to the neurologically derived concept, inhibition. We often fail to realize that within behavioral science and within neurological science there are many levels of discourse. Thus a concept derived from the analysis of linguistic behavior may or may not match one derived from instrumental behavior. A concept that derives from the electrical records made with gross electrodes may or may not jibe with notions derived from microanalysis. Anokhin has a favorite way of talking to his classes about this: "It is such a long distance from the behavior of groups of cells to the behavior of groups of people." As he points out, it is necessary to understand the systematic organization—the *structural* aspects of the arrangement of groups—before *process* at the next level can even be thought about intelligently. I am afraid that in these pages we have often elided the levels in discussing process without coming to grips with organization. This has not been so much the fault of the individuals who have presented their studies as it has been that of the admixture and juxtaposition of presentations that, although they deal in entirely different universes of discourse, yet use a common terminology.

However, even this confusion has its virtues. Because of the hope of rapprochement, experiments are accomplished that would have been undreamed of not long ago. The rigorous shakedown can come later, provided that we are aware that all of the experimental results do not jibe at the moment. I do not think that Roy John's measurements of what he presumes to be the inhibitory neural process have, at this point, much to do with Asratyan's inhibitory process, but I hope that I am wrong. Furthermore, I am convinced that Roy John is correct in his demonstration that slow wave activity can reflect "inhibition" under one environmental circumstance and "excitation" at another. At a neuronal level, even different parts of the neurons are probably behaving quite differently. Axonal impulsive activity and dendritic graded responses have already been dissociated by Jasper and others. I strongly feel that sooner or later we must abandon such overly simple notions as inhibition except as they describe the transactions of neuronal elements. I realize full well that inhibition in the behavioral sense can be used as Kupalov has used it, as a purely descriptive term, but this is not the sense of the meaning as I understand Asratyan. I agree that the seat of the problem toward which the trans-switching experiments are directed lies in neither end of the behavioral events investigated, but between them. I do not believe for a moment, however, that the seat of this is necessarily in the cortex, nor should I describe it simply as a process of inhibition. Some more complicated device, probably hierarchically organized, orders the responses made in each of the situations. The organism may make *plans* to guide his behavior, if you will. These plans could be accomplished by machinery more akin to that found in a computer

than by some simple process of inhibition taking place in a set of cells. Switching, adaptation, and feedbacks with various time delays may well be involved. Such elementary processes can impose structure on the otherwise essentially stimulus-bound random mechanism implicit in the excitation-inhibition model. Ascertaining the constraints that operate on the stochastic process can be accomplished by combining the techniques so beautifully developed by Asratyan with those reported by Roy John, Morrell, Brazier, Killam, and others; perhaps investigators in the Soviet Union have already accomplished this. I should like to know the results of such experiments.

SUMMARY

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Academy of Medical Sciences of the Union of Soviet Socialist Republics, Moscow, U.S.S.R.

I shall not say anything definite in conclusion. As I remarked after my paper, it will be necessary for me to study and think about all the material presented in these pages; only after that will it be possible to combine our opinions and our understanding of these complex subjects.

Therefore I can say in general only that I think that these pages, representing the first large-scale meetings abroad that we Soviet workers have had with foreign investigators, will enable us to understand their representation of Pavlov's school of physiology, the physiology of higher nervous activity, and that is very useful for us. The results, of course, will be of great consequence and will give us new impetus for new experiments and for new ideas.

In this field of science, investigation of the brain is the most important thing.

I hope that our mutual relations after this first experience will become closer and closer, and that we shall have more frequent contact. That is the hope of all Soviet investigators. We sincerely compliment the organizers of the conference on which this monograph is based.

CONCLUDING REMARKS

Gregory Razran
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I have had a truly esthetic experience in noting that orthodox Pavlovianism has moved into the plains of Iowa and Nebraska while, on the banks of the rivers Moskva and Neva, innovations are being introduced into Pavlov's systems. I consider Asratyan's paper an excellent paradigm of experimental ingenuity and interpretative creativity. Psychology is perennially faced with the problem of association versus novelty. Pavlov showed us how conditioning can objectify association and convert it from a mental attribute into a psychobiological evolvent. Now Asratyan is beginning to demonstrate how conditioning can objectify and account for novelty. Like his great teacher, Ivan Petrovich Pavlov, Asratyan is an innovator. I should surely add that all the Soviet contributors to this monograph appear to me to be innovators. Kupalov's concept of "truncated conditioning" is an innovation, Anokhin's "functional system" and "reverse afferentation" are innovations, and I detect similar novelty in the papers of the psychiatrists, Zakusov, Snezhnevsky, and Kerbikov. Innovation is, of course, the pang and the joy and the sign of a growing science. May I quote from a recent editorial in the *Pavlov Journal of Higher Nervous Activity* (March-April, 1959): "At the same time great efforts are being made to interpret Pavlov's writings: to determine whether he was a supporter or an opponent of psychology as an independent science, whether he thought that physiology should absorb psychology. Although these are interesting problems to us, we believe that it is much more important to decide how we ourselves should look at these matters, with due regard for the contemporary level of science. Science does not and cannot stand still."

I am quite sure that I express the feelings of all the United States participants in this Pavlovian monograph in applauding heartily the spirit of this passage from the editorial in the Soviet journal.

IN CONCLUSION

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The over-all impression of the United States participants in respect to the work of our Soviet colleagues is that it is rather spotty: that in some areas they are ahead of us and in others they are not up to us. This may sound like a shocking remark with which to conclude; however, I have also talked with my Soviet friends and have asked them their opinion of the American work, and they say that it is rather spotty.

I think a mutual confession of "spottiness" is one of the healthiest states possible. No one of us has complete superiority in all fields. We both should acknowledge the areas in which we are good and the areas in which we are still deficient.

I thank the participants who have contributed so much under such great pressure: many of them have presented truly brilliant and original papers.

Finally, as some of you know, I am sure, the Russian custom in respect to addressing people progresses from "professor" or "doctor," not to the first-name stage, as it does in this country, but to the use of the patronymic, that is, the given name plus the name "Son of ——— whatever your father's name was."

Hence I conclude by extending personal thanks to Peter Stepanovich Kupalov, whose charm has endeared him to everyone he has met in the United States; to Vasili Vasilievich Zakusov, for his sophistication and the adaptability he has shown; to Peter Kuzmich Anokhin, for the legions of acquaintances and friends he has acquired with such amazing rapidity; to Andrei Vladimirovich Snezhnevsky, whose sense of humor is so delightful; to Oleg Vasilievich Kerbikov, for the quiet efficiency with which he carries out his activities; and, finally to our last formal participant, Esras Asrutovich Asratyan who, at the conference on which this monograph is based, not only had the most dramatic delivery but also demonstrated the greatest solo voice heard in the entire history of Town Hall.

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